**Public Release Summary**
**on**

**Evaluation of the new active**

**DICYCLANIL**

**in the product**

**CLIK® Spray-on Sheep Blowfly Treatment**

**National Registration Authority**
**for Agricultural and Veterinary Chemicals**

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## Foreword

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the NRA works in close co-operation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (Worksafe Australia) and State departments of agriculture and environment.

The NRA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the NRA 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 NRA's publications *Vet Manual: The Requirements Manual for Veterinary Chemicals* and *Vet Requirements Series: Guidelines for Registering Veterinary Chemicals.*

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA and its advisory agencies. It 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 all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the NRA. Alternatively, the reports can be viewed at the NRA Library, Third floor, 10 National Circuit, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.

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# List of abbreviations and acronyms

| | |
|---|---|
| **ADI** | acceptable daily intake (for humans) |
| **ai** | active ingredient |
| **bw** | body weight |
| **cm** | centimetre |
| **$DT_{50}$** | time to 50% dissipation |
| **$DT_{90}$** | time to 90% dissipation |
| **$EbC_{50}$** | concentration at which 50% of biomass is adversely effected |
| **$EC_{50}$** | concentration at which 50% of the test population are immobilised |
| **EQS** | Environmental Quality Standard |
| **ESI** | Export Slaughter Interval |
| **g** | grams |
| **h** | hour |
| **ha** | hectare |
| **HDPE** | high density polyethylene |
| **HPLC** | high pressure liquid chromatography *or* high performance liquid chromatography |
| **IGR** | insect growth regulator |
| **in vitro** | outside the living body and in an artificial environment |
| **in vivo** | inside the living body of a plant or animal |
| **ISO** | International Standards Organisation |
| **kg** | kilogram |
| **Koc** | organic carbon partition coefficient |
| **Kow** | octanol/water partition coefficient |
| **L** | litre |
| **$LC_{50}$** | concentration that kills 50% of the test population of organisms |
| **LD50** | dosage of chemical that kills 50% of the test population of organisms |
| **LOQ** | limit of quantitation |
| **µg** | microgram |
| **mg** | milligram |
| **mL** | millilitre |
| **ML** | megalitres |
| **mm** | millimetre |
| **MRC** | Meat Research Council |
| **MRL** | maximum residue limit |
| **MSDS** | Material Safety Data Sheet |
| **MTD** | maximum tolerated dose |
| **NDPSC** | National Drugs and Poisons Schedule Committee |
| **NOEC/NOEL** | no observable effect concentration/level |
| **PPE** | Personal Protective Equipment |
| **ppm** | parts per million |
| **SUSDP** | Standard for the Uniform Scheduling of Drugs and Poisons |
| **TGAC** | technical grade active constituent |
| **WHP** | withholding period |

# Summary

This publication summarises the evaluation by the National Registration Authority for Agricultural and Veterinary Chemicals of an application for registration of a new product, CLIK® Spray-on Sheep Blowfly Treatment.

The product is based on a new active constituent, dicyclanil, and is to be recommended for use on sheep to provide long-term protection from blowfly strike by *Lucilia cuprina*. Dicyclanil is an insect growth regulator with high specificity against *Diptera* and *Siphonaptera*. CLIK® Spray-on Sheep Blowfly Treatment contains 50g/L dicyclanil.

***Public health aspects***

Based on an assessment of the product's toxicology, it was considered that there should be no adverse effects on human health from the proposed use of dicyclanil in the product CLIK® Spray-On Sheep Blowfly Treatment.

The National Drugs and Poisons Scheduling Committee (NDPSC) recommended that dicyclanil be placed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), except in preparations containing 5 per cent or less of dicyclanil (which would include CLIK® Spray-On Sheep Blowfly treatment). Appropriate safety directions have been recommended for inclusion on the product label.

Dicyclanil has moderate acute oral toxicity (rats $LD_{50}$ = 560 mg/kg), and low dermal (rats $LD_{50}$ > 2000 mg/kg) and inhalational toxicities (rats $LC_{50}$ = 3184 mg/mg$^3$). It is a slight skin and eye irritant but is not a skin sensitiser. A formulation closely similar to CLIK® Spray-on Sheep Blowfly Treatment has low acute oral and dermal toxicity (rats oral and dermal $LD_{50}$ > 5000 mg/kg), is a slight skin and eye irritant, and is not a skin sensitiser.

Following repeated administration of dicyclanil, decreased weight gain and/or decreased food consumption were common in dogs, rats and mice. Liver was the main target organ for toxicity in all species with increased liver weights, necrosis and increased size of liver cells (hepatocellular hypertrophy) being observed.

Pigmentation of the cells lining the nose (olfactory epithelium) was seen in rats and mice and in the adrenal glands of mice. In female mice there was an increased incidence of liver tumours (hepatocellular carcinoma and benign hepatoma) at doses of dicyclanil which exceeded the maximal tolerated dose (MTD). In male mice, and in rats and dogs, dicyclanil did not show any sign of carcinogenicity. Genetic damage was not evident in a range of assays.

Findings related to testicular degeneration were obtained in rats and dogs in a few studies. However, these effects were limited primarily to short-term, high dose studies or to individual animals displaying overt toxicity to dicyclanil. Although the findings of testicular effects in both rats and dogs are of some concern, these concerns are allayed by a two-generation reproduction study in rats, which found no evidence of reduced male fertility or testicular effects despite approximately 30 weeks of treatment. There were no treatment-related foetal malformations in rats and rabbits, but dicyclanil affected foetal development at high doses, which were toxic to the parental animals.

*Chemical residues in food*
Dicyclanil is a substituted pyrimidine compound, 4,6-diamino-2-cyclopropylaminopyrimidine -5-carbonitrile (CGA 183893).

Appropriate residue and metabolism studies were submitted for evaluation in accordance with the *Interim Requirements for the Registration of Agricultural and Veterinary Chemical Products* to support use of the product. Nine residue trials were conducted that addressed the proposed use pattern.

The residue data and use pattern indicate that a 28-day slaughter withholding period (WHP) is appropriate for sheep. The metabolism and residue data show that when the product is used in accordance with Good Agricultural Practice, the proposed Maximum Residue Limits (MRLs) for dicyclanil should not be exceeded and consumption of tissues from treated animals is unlikely to result in the ingestion of residues exceeding the established Acceptable Daily Intake (ADI).

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

**TABLE 1**

| Compound | Food | MRL (mg/kg) |
|---|---|---|
| **DELETE:** | | |
| **4,6-Diamino-2-cyclopropylaminopyrimidine-5-carbonitrile** | **Sheep meat**<br>**Sheep, Edible offal of** | **T1**<br>**T1** |
| **ADD:** | | |
| **Dicyclanil** | **Sheep meat**<br>**Sheep, Edible offal of** | **0.3**<br>**0.3** |

and

**TABLE 3**

| Compound | Residue |
|---|---|
| **DELETE:** | |
| **4,6-Diamino-2-cyclopropyl-aminopyrimidine-5-carbonitrile** | **Sum of 4,6-Diamino-2-cyclopropyl-aminopyrimidine-5-carbonitrile and its triaminopyridyl metabolite, expressed as 4,6-Diamino-2-cyclopropyl-aminopyrimidine-5-carbonitrile** |
| **ADD:** | |
| **Dicyclanil** | **Dicyclanil and its triaminopyridyl metabolite, expressed as dicyclanil** |

*Implications for trade*

Dicyclanil is not registered for use on food producing animals in the major markets for Australian sheep commodities. In the absence of a reciprocal trade agreement, nil residues will be required by export markets. However, as indicated by the proposed MRLs of 0.3 mg/kg for sheep meat and edible offal, finite residues are expected at the label slaughter WHP of 28 days.

Residue data indicate that tissue residues have generally depleted to less than the Limit of Quantitation (LOQ) (0.01 mg/kg) by 4 months post-treatment. To ensure residues of dicyclanil are not detected by residue surveillance programs in importing countries, an export slaughter interval (ESI) of 120 days has been proposed by the Meat Research Corporation. The Australian label will direct users to check overseas standards when dicyclanil-treated sheep are to be slaughtered for export.

Environmental quality standards for dicyclanil residues arising from scouring wool have not been established in Australia's major wool trading partners. The likely hazard arising from wool scour effluent has been assessed using various models based on a worst-case situation, data from wool residue studies and the use of the product according to label directions and according to Good Agricultural Practice. The assessment concludes that a 12-week wool withholding period will minimise any hazard to the environment in places outside Australia.

*Occupational health and safety*

Based on the occupational health and safety assessment, it was considered that CLIK® Spray-On Sheep Blowfly Treatment (Clik) can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

Dicyclanil is not listed as hazardous substances in the *NOHSC List of Designated Hazardous Substances*. Novartis Animal Health Australasia Limited (Novartis) has determined dicyclanil to be a hazardous substance based on acute oral and inhalation toxicity. Substances containing dicyclanil are hazardous when it is present at concentrations = 25%.

Novartis has determined CLIK® not to be a hazardous substance based on the concentration of dicyclanil in the formulation. The product will be formulated in Australia using imported technical grade active constituent (TGAC).

Dicyclanil technical (powder) is packaged in 20-kg quantities in a polyethylene bag inside a steel drum. CLIK® will be sold in 5 L and 20 L packs. The 5 L pack will be in HDPE bottles and the 20 L quantity will be packed in HDPE drums. Laboratory staff (testing the TGAC), formulators and packers could be exposed to the TGAC and the product. Transport, storage and retail workers will also handle the product but could only be exposed to the product if packaging is breached.

The acute toxicity, irritancy and dermal sensitisation properties of CLIK® have not been investigated. However, a similar product containing 5% dicyclanil has low oral and dermal toxicity (oral and dermal $LD_{50}$ >5000 mg/kg, no deaths) in rats, is a slight skin and eye irritant in rabbits and is not a skin sensitiser in guinea pigs.

The product is to be used undiluted, as a low-volume spray treatment onto or near areas where protection is required. The dose volume is determined by the weight of sheep being treated. The recommended dose volume is <0.7-2 mL product/kg live weight to achieve a dose rate of

<35-100 mg dicyclanil/kg live weight. This dosage protects sheep against flystrike for 18 to 24 weeks after treatment.

The risk assessment indicates that elbow-length rubber gloves are required when opening the container and using the product.

***Environmental aspects***

Topical application of dicyclanil to sheep may result in some contamination of the environment on the property where the animals are treated, but the main source of environmental contamination will be residues remaining in wool at shearing, most of which will be removed in effluent from the wool scouring process.

***Environmental fate***

Dicyclanil is hydrolytically stable, with a calculated hydrolysis half-life in excess of one year at 20-40°C. The substance is slightly photodegradable under aqueous conditions in the absence of sensitisers, but fairly to readily photodegradable in the presence of sensitisers (half-life = 2.5-5.1 days). The main photoproduct was the dealkylation metabolite CGA 297107, which was also the principal metabolite detected in an aerobic metabolism study with $^{14}$C-labelled dicyclanil in a loam soil.

The latter study indicated half-lives for dicyclanil and CGA 297107 at 20°C of 1.5 and 157-173 days, respectively, thus dicyclanil is readily degradable in soil under moist, aerobic conditions, but CGA 297107 is only slightly degradable under the same conditions. While significant mineralisation of the substance ultimately occurred in the aerobic soil metabolism study, dicyclanil was classified as "not readily biodegradable" according to a standard Ready Biodegradability test.

Dicyclanil is very slightly volatile and unlikely to evaporate from soil or water. Laboratory studies with 5 soils found $K_{OC}$ values in the range 89-273 (average 136) for adsorption, indicating that dicyclanil is likely to have medium to high mobility in soil. An aged soil column leaching study with 2 soils found that very little radioactivity was present in the leachate, but that some movement down the column had occurred (residues were largely restricted to the top 14 or 20 cm of the column with a loamy sand or loam soil, respectively). Thus in soil under field conditions, dicyclanil would be expected to degrade rapidly, with little downward movement of the parent substance. Based on its octanol/water coefficient ($K_{OW}$), dicyclanil is unlikely to accumulate in fish.

***Fate following application to wool***

When applied to sheep by the pour-on method (as proposed), retention was found to be ~90-98% of the applied amount, whereas retention was much poorer with jetting application (39-59%). Absorption of the applied dose was ~4% with pour-on application, absorbed residues largely being recovered in urine and faeces within 7 days of application, and a similar amount of residues were evidently lost in rub-off of the dried spray.

Studies of the fate of the substance in wool found that with pour-on application, a small amount of movement of the applied substance occurred within the fleece, but that residues largely remained in the treated portion of the wool (i.e. tip of the growing staple). Dissipation (affected by growth dilution effects as well as degradation, absorption and movement within or loss from the fleece) was much more rapid where sheep treated by pour-on application of a dicyclanil formulation (similar, but not identical, to that proposed for CLIK®) were exposed to repeated simulated rain events, rather than being kept continually dry.

Dissipation half-lives calculated by Environment Australia for whole staples in the treated backline area with pour-on application were 53.2 to 70.7 days for sheep kept dry and 6.5 to19.9 days for sheep exposed to 500-1000 mm rain. Calculations by Environment Australia for dissipation following jetting application indicated half-lives of 69.2 to 82.6 days, but were much longer (135 to 187 days) if growth dilution effects were removed by correcting for the increase in staple length at each sampling occasion. None of the sheep in these studies were regularly exposed to sunlight, and the rate of degradation is potentially faster where there is opportunity for photodegradation to occur.

Wool from sheep which had been shorn 12 weeks after treatment with a formulation similar (but not identical) to CLIK® was found to contain 107 mg dicyclanil and 66.3 mg CGA 297107 per kg wool (i.e. lower dicyclanil residues than expected from the above studies, with much more of the metabolite than encountered in the other wool studies). A dicyclanil half-life of 30 days was estimated from these results, the more rapid degradation in this situation than in the studies discussed above presumably being due to exposure to sunlight as well as 169 mm rain. Both substances were found to be associated with the aqueous discharges from a pilot scale scouring process and there was little association with the wool, wool wax or dirt fractions. Thus most dicyclanil and CGA 297107 residues in wool are likely to reach sewage effluent as a result of the scouring process.

***Environmental effects***

Studies provided to Environment Australia show that dicyclanil is slightly toxic by acute oral exposure and practically non-toxic by subacute dietary exposure to the bird species Japanese quail (*Coturnix coturnix japonica*).

Acute toxicity tests with dicyclanil indicated that both substances are at most slightly toxic to the fish species rainbow trout (*Onchorynchus mykiss*) and bluegill sunfish (*Lepomis macrochirus*) and a limit test of the toxicity of the metabolite CGA 297107 to rainbow trout also indicated at most slight toxicity to this species. Toxicity tests with dicyclanil and the daphnid *Daphnia magna* indicated that with acute exposure, dicyclanil was moderately toxic to daphnids, but in each case the NOEC was much lower than the $EC_{50}$ for immobilisation. A toxicity test with the metabolite CGA 297107 indicated it was practically non-toxic to *D. magna*. with acute exposure.

A test of the chronic exposure and reproductive toxicity of dicyclanil indicated greater toxicity to adult daphnids (21-day $EC_{50}$ in the range 0.060-0.19 $mg.L^{-1}$ nominal concentrations) and much greater toxicity to reproduction (NOEC < 0.0019 $mg.L^{-1}$ based on statistical comparison with the control, though the practical effect of this difference appeared minor). 72-hour growth inhibition tests indicate that dicyclanil and the metabolite CGA 297107 are both slightly toxic to freshwater green algae (*Scenedesmus subspicatus* and *Selenastrum capricornutum*).

Toxicity studies with dicyclanil and the earthworm species *Eisenia foetida foetida* indicated slight toxicity with 14 days exposure. An activated sludge respiration inhibition test indicated that dicyclanil has low toxicity to sludge microorganisms.

Thus chronic/reproductive toxicity to *Daphnia magna* appears the most sensitive indicator of toxicity for this substance, which is not inconsistent with its mode of action as an insect growth regulator.

***Environmental hazard***

Environment Australia concludes that residues reaching land or inland aquatic situations either on properties where sheep are treated or as a result of disposal of scour effluent on land is unlikely to present a significant hazard arising to land or aquatic organisms.

Residues arising from ocean sewerage effluent discharge are unlikely to present an aquatic hazard once they are adequately diluted, but residues under various usage scenarios are sufficiently high that a localised hazard may arise near the discharge point because dicyclanil concentrations in the undiluted effluent may exceed chronic toxicity NOECs.

Depending on the rate of degradation of residues in effluent moving through the Werribee sewerage treatment plant, there is also a possibility of residues in effluent reaching ponds containing daphnids, where impacts due to chronic toxicity could occur. Environment Australia would therefore wish to ensure usage shortly before shearing is minimised. Promotion of the product for use off-shears to 6 weeks after shearing, together with pricing recognising prolonged control, should assist in this regard. However, due to uncertainties about the chronic toxicity endpoint for aquatic invertebrates and because of the possibility of an additional contribution from cyromazine to aquatic toxicity in the same environment, Environment Australia recommends that an additional margin of safety be provided by a shearing withholding period of 12 weeks (assuming use in the months approaching shearing is $\leq$ 10% of total use of the product).

Trade considerations are also relevant to deciding an appropriate shearing withholding period, as an assessment of the hazard arising from wool scour effluent in rivers based on a worst case situation in the UK indicates that mean residues in Australian wool need to be restricted to 1.1 $mg.kg^{-1}$ to meet an Environmental Quality Standard of 0.2 $\mu g.L^{-1}$ in river water. Environment Australia believes that a shearing withholding period of at least 12 weeks is necessary to meet this requirement at this EQS and notes that a longer withholding may be specified because of these trade considerations.

***Efficacy and safety***

Scientific studies conducted in Australia were presented to support the claim of protection of sheep from blowfly strike by *Lucilia cuprina* for 18 to 24 weeks either off-shears or on sheep with any wool length.

Scientific experts from the State's Department of Agriculture/Primary Industries assessed the submitted studies and found them to be sufficient to support the proposed label claims for the product.

Dicylanil is an insect growth regulator (IGR) effectively preventing egg hatching and lethal against early stage diptera larvae ($1^{st}$ and $2^{nd}$ instar). Efficacy of dicyclanil against *Lucilia cuprina* was established in two *in vitro* studies and a series of *in vivo* studies including three larval implant trails and three animal house trials.

Efficacy of dicyclanil in the product CLIK® Spray-on Sheep Blowfly Treatment was further confirmed in the field with extensive field trials in Australia over three consecutive years comprising dose determination studies covering 12,512 lambs at 22 trial sites in the first year, dose confirmation studies covering 10,286 sheep at 19 trial sites in the second year; and dose confirmation studies covering 10,253 sheep (>6 weeks off-shears) at 16 trial sites and 3,942 sheep (off-shears) at 5 sites in the third year.

No adverse effects were recorded in any of the clinical field trials. In addition a detailed safety study demonstrated that the product applied up to ten times the recommended dose had no adverse systemic effect or effect to the skin. A further study demonstrated that the product when used according to the label directions had no deleterious effects on leather quality.

***Recommendation***

Based on above the NRA recommends that CLIK® Spray-on Sheep Blowfly Treatment when used according to product label directions:

- is effective for the purposed for which it is to be recommended and safe for the intended species;
- would not be an undue hazard to users of the products, not be likely to have an unintended direct or indirect effect that is harmful to humans;
- would not be likely to have an unintended effect that is harmful to animals, plants or to the environment; and
- would not unduly prejudice trade.

# Introduction

The purpose of this document is to provide a summary of the data reviewed, and an outline of regulatory considerations for the proposed registration of the chemical dicyclanil for use as an ectoparasiticide in sheep. The information provided herein presents only the conclusions reached by various expert reviewers after consideration of the scientific database. All trial data and methods of assessment presented for evaluation were conducted to accepted scientific principles and of standard publishable in refereed scientific journals.

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 dicyclanil and now invites public comment before deciding whether to approve this product for use in Australia. This information contained in this document is provided for public comment.

The deadline for comments is 1 September 1998. Comments should be sent to

[redacted]

***Applicant's details***
Novartis Animal Health Australasia Pty Ltd
140150 Bungaree Road
Pendle Hill NSW 2145

***Justification for use***
CLIK® Spray-On Sheep Blowfly Treatment is intended for use in sheep for the protection of sheep, either off-shears or with any length wool against fly strike (*Lucilia cuprina*) for 18 to 24 weeks.

***Product details***
CLIK® Spray-On Sheep Blowfly Treatment contains 50g/L of the active dicyclanil and is to be presented as a 5L and 20L pack size. The formulation of the product takes place at NRA licensed manufacturing plants in Australia.

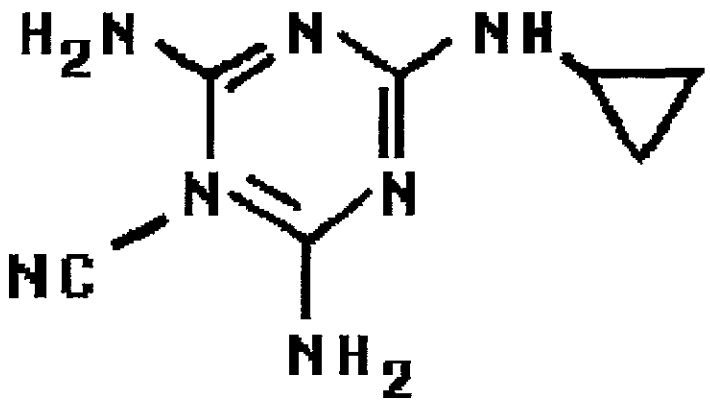
CLIK® Spray-On Sheep Blowfly Treatment is currently registered with a closely similar use pattern in New Zealand.

# Chemistry and Manufacture

***Active constituent***

The chemical active constituent dicyclanil and has the following properties:

| | |
|---|---|
| Common name: | dicyclanil (ISO draft) |
| Chemical name: | 4,6-diamino-2-cyclopropylamino-pyrimidine-5-carbonitrile |
| CAS Registry Number: | 112636-83-6 |
| Empirical formula: | $C_8H_{10}N_6$ |
| Molecular weight: | 190.2 |
| Physical form: | fine powder |
| Colour: | white |
| Odour: | slightly to acetic acid |
| Melting point: | 250.5-252.4°C (523.7-525.6K) with thermal decomposition |
| Density: | 1.32 x 103 kg/$m^3$ |
| Octanol/water partition: | $logP_{ow}$ = 0.51 at pH 5.0 and 25°C |
| | $logP_{ow}$ = 0.69 at pH 7.1 and 25°C |
| | $logP_{ow}$ = 0.68 at pH 9.0 and 25°C |
| Vapour pressure at 25°C: | 3.2 x $10^{-8}$ Pa (extrapolated) |
| Structural formula: | |



# Toxicological Assessment

The toxicological database for dicyclanil, which consists primarily of toxicity tests conducted using animals, is 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.

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective, however, adverse findings in animal species are assumed to represent potential effects in humans unless convincing evidence of species specificity is available.

Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which 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***

Dicyclanil is absorbed orally in rats and within 24 h, most of the absorbed compound is excreted in the urine. Dermal absorption is low. Metabolism is rapid and up to 12 metabolites are found in the urine, faeces and tissues. The major metabolic pathway is by oxidative cyclopropyl-ring opening followed by oxidation of the a-carbon.

***Acute studies***

Dicyclanil had moderate acute oral, and low dermal and inhalational toxicities in rats. In rats, the oral $LD_{50}$ was 560 mg/kg in males, the dermal $LD_{50}$ was greater than 2000 mg/kg, and the inhalational $LC_{50}$ was 3184 mg/m$^3$. In female rats given a single oral dose of dicyclanil at 500 mg/kg, there were 3/5 deaths. It was a slight skin and eye irritant in rabbits. It did not induce sensitisation by topical contact in guinea pigs.

A formulation closely similar to CLIK® Spray-on Sheep Blowfly Treatment, which contains dicyclanil 50 g/L, has low oral and dermal toxicity (oral and dermal $LD_{50} > 5000$ mg/kg, no deaths) in rats, is a slight skin and eye irritant in rabbits, and is not a skin sensitiser in guinea pigs. Skin reddening or inflammation (erythema/oedema) was seen in rats and rabbits. In rabbit eye, irritation was seen in the conjunctiva. The minor differences between the formulation tested and that to be registered are considered unlikely to alter the acute toxicity profile of the product.

***Short-term studies***

Studies were carried out in rats with dicyclanil given orally by gavage (0, 10, 50 or 200 mg/kg/day), in diet (0, 10, 48 and 160 mg/kg/day) or by dermal application (0, 5, 30, 300 and 1000 mg/kg/day), for four weeks. Dose-related decreases in weight gain and food consumption were seen. Other effects included increased liver weight and cell size (hypertrophy), increase in blood ALT (a marker for liver toxicity), cholesterol and alkaline phosphatase levels, and testicular atrophy and immature function of the prostate. Most of these effects were seen in the high dose groups.

A study was conducted in dogs (0, 6, 30 and 55 mg/kg/day) with dicyclanil in the diet for four weeks. The effects, seen mostly in the high dose groups, included vomiting, tremor, slight apathy, difficulty in breathing (dyspnoea), decreased feed consumption and loss of weight, decreased ALT and increased alkaline phosphatase, presence of protein in urine, decreased testicular weights, increased liver and kidney weights, liver lesions, slight to moderate degeneration of the testes, atrophy in the thymus, and renal tubular dilation.

***Subchronic studies***

Rats were given 0, 5, 25, 125 or 250 parts per million (ppm), equivalent to 0, 0.3, 1.6, 8.2 or 33 mg/kg/day dicyclanil, in the diet for 3 months. Feed consumption and weight gain were slightly decreased at 25 ppm and above. Plasma glucose and total plasma protein levels were reduced in the 125 and 250 ppm groups. At 250 ppm, increased kidney and testicular weights were observed in males and increased liver weights in females. In males increases in epididymis weights were observed at 25 ppm and above. All the changes observed were reversible after 4 weeks. There were no treatment-related abnormalities seen by gross inspection or by microscopic examination of tissues. The NOEL was 5 ppm (0.3 mg/kg/day).

Dogs were administered 0, 20, 100, 500 or 1500 ppm (0, 0.6, 3, 16 or 44 mg/kg/day) dicyclanil in the diet for 3 months. Vomiting, blood stained faeces, and neurological signs including slight ataxia, raised tails and frequent shaking of the body were observed in the high dose group (1500 ppm). One high dose male showed convulsions and died during the study.

Reductions in feed consumption and weight gain, slight anaemia, and increased platelet counts were detected in the high dose group. Increases in plasma cholesterol and phospholipid levels, and decreases in plasma protein and albumin concentrations were observed at 100 ppm or above. At the high dose, the weights of liver, adrenal and kidney were increased and the weights of thymus, spleen and testes decreased. The weights of hearts were decreased at 500 and 1500 ppm. Slight to moderate inflammation with fibrosis of the liver was observed in the high dose group, and enlarged liver cells (hepatocytes) were detected in all treated female groups and high dose male group. Slight atrophy of the spleen occurred at 500 and 1500 ppm. In males, atrophy of mesenteric lymph nodes and prostate was observed at 1500 ppm, and thymus atrophy at 500 and 1500 ppm.

A marked decrease in sperm production (decreased spermatogenesis) was found in the high dose males, associated with tubular atrophy. In females, inflammatory changes and increased number of cells lining urinary bladder were found at 100 ppm and above. A NOEL was not established, as the liver lesions were observed in all treated female groups.

***Long-term studies***

Albino mice were treated with dicyclanil at 0, 10, 100, 500 and 1500 ppm in the diet for 18 months (doses for males/females: 0, 1.1/1.1, 12/12, 59/64 and 212/200 mg/kg bw/day). Increased mortality was seen at 1500 ppm and decreased weight gains at 500 and 1500 ppm. The weights of liver, kidney and adrenal gland were increased at 500 ppm and the spleen weights increased at 100 and 500 ppm. Pathological examination found an increased incidence of enlargement or lumps in the liver at 500 and 1500 ppm, enlarged spleens in males at 1500 ppm, dilatation of uterus in females at doses 100 ppm and above, and increased pulmonary nodules in females at 1500 ppm.

Microscopic study revealed that at 100 ppm or above, liver had cell pigmentation (haemosiderin), necrosis, increased cell size (hypertrophy) and changes indicative of cell division. Pigmentation was also seen in the cells lining the nose (olfactory epithelium) at 100 and 500 ppm and in the adrenal glands at 500 ppm. The number of bone marrow cells was increased at 500 ppm. The incidence of liver tumours was increased in females: benign hepatoma at 500 ppm and hepatocelluar carcinoma at 1500 ppm. The NOEL for this study was 10 ppm (1.1 mg/kg/bw/day).

Albino rats were treated with dicyclanil at 0, 5, 25, 125 and 500 ppm in the diet for 24 months (doses for males/females: 0, 0.2/0.2, 1.0/1.2, 4.8/6.0 and 22/26 mg/kg bw/day). Decreased weight gain and food consumption were observed at 500 ppm. At 500 ppm, a few parameters of red blood cells were slightly increased (volume and haemoglobin concentration), and monocyte count and eosinophil count were decreased. In males the blood levels of inorganic phosphorus were increased at 125 and 500 ppm, and triglyceride levels decreased at 500 ppm. At 500 ppm, the number of cells of the exocrine pancreas (hyperplasia) was increased in males and biliary cysts increased in females. Pigmentation of olfactory epithelium was seen at 25 ppm and above doses. Dicyclanil did not show any evidence of carcinogenic activity. The NOEL for this study was 5 ppm (0.2 mg/kg bw/day).

Beagle dogs were treated with dicyclanil at 0, 5, 25, 150 and 750 ppm (doses for males/females: 0.2/0.2, 0.7/0.8, 4.4/5.1 and 23/23 mg/kg bw/day) in the diet for 12 months. At 750 ppm, two animals did not survive to the end of the study, animals ate less but gained weight normally, vomiting was observed, and the platelet count was increased. Blood cholesterol was increased in males at 150 and 750 ppm and in females at 750 ppm. Blood calcium in males and triglycerides in females were decreased at 750 ppm. Alkalinization (increase in pH) of urine was observed at 750 ppm. Liver weights were increased at 750 ppm.

In females that received 150 and 750 ppm of dicyclanil, heart weights were decreased. The changes at microscopic examinations were confined to the two dogs which died or were moribund in the 750 ppm group. Necrosis of the liver, lesion of the kidneys (acute tubular lesion), a mass due to thrombus in a peritoneal blood vessel with haemorrhagic content in the abdominal cavity, degeneration of germinal cells of testis associated with reduction of spermatozoa (in the lumen of epididymis) and prostatic atrophy were noted. The NOEL for this study was 25 ppm (0.7 mg/kg bw/day).

***Reproduction and developmental studies***

In a fertility study, oral administration of dicyclanil by gavage at 150 mg/kg/day for 4 weeks (5 days/week) in male rats reduced food intake, weight gains and testicular weights. Dicyclanil also caused reduced sperm production and reduction in the fertility of treated males, but the effects were reversible although the recovery was slow.

In a two-generation reproduction study, with two litters in each generation, male and female rats were administered dicyclanil in the diet at 0, 5, 30, 200 and 500 ppm. Reproduction was unaffected by treatment. In both the parents and the first generation adults, food consumption and weight gains were reduced at 200 and 500 ppm. No treatment related effects were observed in pup development except reduced pup weights at 500 ppm. The NOEL was 30 ppm (1.5 mg/kg bw/day).

The teratogenic potential of dicyclanil was studied in pregnant rats treated, by gavage, with 0, 1, 5, 25 or 75 mg/kg bw/day of dicyclanil during the period of foetal organ development.

Animals gained less weight at 75 mg/kg bw/day and ate less at 25 and 75 mg/kg bw/day. Treatment related effects in the foetus were confined to the high dose group where the number of foetuses per litter and foetal weights were reduced, and early resorption was increased.

Increased incidences of changes in kidney (renal pelvic dilation) and bone abnormalities (sternebral defects and slightly delayed skeletal ossification) were observed in foetuses of this group. Two foetuses, from two litters of the high dose group, had displaced hip bone (pubis). There were no treatment-related malformations. The maternal NOEL was 5 mg/kg/day and the fetal NOEL was 25 mg/kg/day.

In a teratogenicity study in rabbits, pregnant rabbits were administered 0, 1, 3, 10 or 30 mg/kg/day dicyclanil by gavage during the period of foetal organ development. Maternal animals ate less at 30 mg/kg/day and gained less weight at 10 and 30 mg/kg/day. The only changes observed in foetuses were reduced foetal body weight and slightly delayed bone development (ossification) in the high dose group. There were no treatment-related malformations. The maternal NOEL was 3 mg/kg/day, and the foetal NOEL was 10 mg/kg/day.

***Genotoxicity***
Negative results were obtained in a range of studies to assess gene toxicity. The assays conducted were gene mutation (*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, *Escherichia coli* WP2uvrA, and Chinese hamster lung cells V79 *in vitro*), chromosomal effects (Chinese hamster ovary cells in culture and micronucleus formation in mice *in vivo*), and DNA damage (rat primary hepatocytes *in vitro*).

## Public health standards

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

The NDPSC recommended that dicyclanil be placed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), except in preparations containing 5 per cent or less of dicyclanil. Appropriate safety directions have been recommended for inclusion on the product label.

***NOEL/ADI***
The most sensitive species tested was the rat with a NOEL of 0.2 mg/kg bw/day in a 24 month study. In order to calculate an 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 from 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 0.002 mg/kg bw/day was established for dicyclanil.

## Residues Assessment

This section provides evaluation of the data submitted by the applicant to support establishment of MRLs for dicyclanil in sheep meat and edible offal.

The applicant proposes use of the product as a spray-on application for the control of blowfly strike. The proposed nominal dose rate is 35 to 100 mg dicyclanil per kg bodyweight depending on the weight group (surface area) of the animals. The re-treatment interval is expected to be a minimum of 18 weeks.

***Metabolism studies***
Studies were conducted in rats and sheep. The metabolic patterns in rats and sheep were qualitatively similar with the major residue detected being dicyclanil (in muscle and fat) and metabolite CGA297107 (in kidney and liver).

***Rats***
In rats orally dosed with $^{14}C$- labelled dicyclanil, >93% of the dose excreted within 24 hours of the last dose (>79% in urine; 6-13% in faeces). Greater than 80% of the dose was absorbed from the gastrointestinal tract. The magnitude of residues was greatest in the liver followed by kidney, muscle and fat. The metabolite profile for urine, faeces and tissues revealed up to 12 metabolites. In urine and faeces the major components were polar metabolites with unchanged parent accounting for only 2-7% and 0.1-1% respectively.

***Sheep***
Following intra-ruminal administration of dicyclanil to sheep, peak dicyclanil plasma concentrations were achieved after 6 hours; the dicyclanil plasma elimination half-life approximated 1 day. Approximately 6 and 4% of the dose was recovered as unchanged parent in the urine and faeces respectively.

After intravenous administration of dicyclanil to sheep, parent compound accounted for less than 1% of the dose recovered in urine and 33% of the dose in faeces.

Following jetting of sheep with $^{14}C$-dicyclanil, the radioactive residues on the wool and present in run-off were almost exclusively unchanged parent. Less than 2% of the dose was absorbed dermally. The highest tissue residues were observed 1 day post-dose in the liver. The elimination half-lives for dicyclanil were not sex-dependent.

Urine and faeces accounted for approximately 0.6 and 0.9% of the retained dose respectively. In faeces, 90% of the radioactivity was composed of the parent dicyclanil, the triaminopyridyl metabolite (CGA297107) and the propionamide derivative of dicyclanil (MET 1U). In urine, equal proportions of dicyclanil and triaminopyridyl metabolite were found, together with a small amount of MET 1U and the propionic acid metabolite (MET 5U).

Fat residues were predominantly dicyclanil together with small amounts of the triaminopyridyl metabolite. Similarly, in muscle, dicyclanil was the major component; lower levels of the triaminopyridyl metabolite and MET 1U or the ring-opened propionamide compound were also reported. In liver and kidney the major metabolites identified were the triaminopyridyl compound together with lower levels of the parent and MET 1U.

Results for sheep treated with a $^{14}$C-dicyclanil pour-on formulation were similar to those following jetting. In particular, the metabolite profile for the various tissues was similar to that obtained in the jetting study.

The metabolism of dicyclanil in rats and sheep showed similar pattems of degradation although the distribution of individual metabolites differed. In both species, metabolism of dicyclanil was by oxidative cyclopropyl-ring opening followed by further oxidation to yield the triaminopyridyl metabolite (CGA297107), the propionamide derivative of dicyclanil (MET 1U) and the propionic acid metabolites (MET 3U and MET 5U).

Collectively the submitted metabolism studies indicated that dicyclanil is extensively metabolised and excreted moderately rapidly in sheep.

***Residue definition***

In sheep, tissue residues are comprised predominantly of parent compound and metabolite CGA297107. Analytical procedures using HPLC can determine both components. It is therefore appropriate to define the residue as:

| | |
|---|---|
| Dicyclanil | Sum of dicyclanil and its triaminopyridyl metabolite expressed as dicyclanil |

***Analytical methods***

The principle of the analytical procedure is to extract dicyclanil, clean-up the extract and quantitate by HPLC. Studies indicated that incurred residues in tissues were stable for the period of the residue studies.

***Residue trials***

*Sheep*

Nine trials were conducted that addressed the proposed use pattern. Anomalously high values were sometimes encountered for subcutaneous fat residues. These appear to be due to contamination from dicyclanil present on the fleece at slaughter, although there was considerable inter-animal variation.

Merino sheep, two-weeks off shears, were treated topically with 5% dicyclanil formulation at *ca.* 50 mg/kg bw. Groups were sacrificed at 7, 14, 21, 28 and 42 days after treatment. Maximum tissue residues of dicyclanil were in liver and declined from 0.23 mg/kg at day 7, through 0.18 mg/kg at day 28 to <0.01 mg/kg at day 42. Kidney levels were consistently below 0.3 mg/kg. At 28 days, the maximum fat and muscle residue levels were both <0.1 mg/kg.

In a separate study involving two trials, fattening lambs treated topically at 100 or 200 mg/kg bw (2× and 4× the label rate) were sacrificed at 3, 7, 14, 21, 28 and 35 days post-treatment. The maximum residue levels in animals dosed at 2× the label rate after 28 days were 0.07 mg/kg (liver), 0.11 mg/kg (kidney), <0.01 mg/kg (fat) and 0.04 mg/kg (muscle). For the group dosed at 4× the label rate the corresponding values were 0.28, 0.25, <0.01 and 0.14 mg/kg for liver, kidney, fat and muscle respectively.

The effect of wool length on the residue levels was addressed in a study involving four trials on merino sheep 0 and 6 weeks off-shears. Animals dosed at 2× or 4 × the label rate were

sacrificed at 7, 14, 21, 28 and 56 days after treatment. There were no significant differences between groups with different wool lengths. Residue levels peaked at 7 to 14 days post-treatment. By 28 days post-treatment the maximum residue levels for the 2× treatment groups were 0.24, 0.21, 0.03 and 0.13 mg/kg for liver, kidney, renal fat and muscle respectively.

Cross-bred lambs and merino sheep were treated topically with 5% dicyclanil formulation at *ca.* 100 and 50 mg/kg bw for the lambs and merino sheep respectively. For each of the two trials groups of animals were sacrificed at 7, 28, 56, 84 days and 4 months after treatment. At 28 days post-treatment, the maximum residue levels were 0.05 mg/kg (liver), 0.09 mg/kg (kidney), 0.05 mg/kg (fat) and 0.02 mg/kg (muscle). By 4 months post-treatment the tissue residues had generally depleted to less than the analytical limit of quantitation.

***Withholding period statements***

Withholding periods for use of CLIK® SPRAY-ON Sheep Blowfly Treatment should be established as follows:

> WITHHOLDING PERIOD: MEAT: DO NOT USE less than 28 days before slaughter for human consumption.
>
> WITHHOLDING PERIOD: MILK: DO NOT USE on sheep which are producing or may in the future produce milk or milk products for human consumption.

***Dietary intake***

Dietary intake calculations indicate that the theoretical maximum daily intake of dicyclanil from sheep meat and offal does not exceed the Australian ADI for dicyclanil of 0.002 mg/kg/day, and is thus safe for human consumption.

## Assessment of Overseas Trade Aspects of Residues in Food

*Commodities exported*
Data from the Australian Meat and Livestock Corporation identify two specific export commodities, lamb and mutton. The major destinations countries for Australian sheep meat in 1996 for mutton were South Africa (24,940 tonnes), Saudi Arabia (15,748 tonnes), Japan (15,682 tonnes) PNG (11,578 tonnes), USA (9,404 tonnes) and for lamb were USA (10,636 tonnes), PNG (8,832 tonnes), UK (5,000 tonnes) Japan (4,811 tonnes), Dubai (4,684 tonnes).

*Overseas registration status and MRLs*
CLIK® Spray-On Sheep Blowfly Treatment is currently registered with a closely similar use pattern in New Zealand. New Zealand MRLs are set at 0.1mg/kg for both offal and meat.

Dicyclanil is not registered for use on food producing animals in the Australia's major markets for sheep commodities and there are no MRLs or tolerances established in countries importing Australian sheep meat commodities.

*Codex Alimentarius Commission MRLs*
There are no CODEX MRLs for dicyclanil in food producing animals. Novartis intends to apply for Codex MRL as soon as registration is obtained in two countries.

*Australian MRLs*
The MRLs proposed herein for Australia are:

| | |
|---|---|
| Sheep Meat | 0.3 mg/kg |
| Sheep, Edible offal | 0.3 mg/kg |

*Potential risk to trade*
In the absence of MRLs or tolerances established in countries importing Australian sheep meat commodities it is proposed the Limit of Quantitation (LOQ) (0.01mg/kg) for dicyclanil be adopted as the export standard.

As indicated by the proposed MRLs of 0.3 mg/kg for sheep meat and edible offal, finite residues are expected at the label slaughter WHP of 28 days. Residue data indicate that tissue residues have generally depleted to <LOQ (0.01 mg/kg) by 4 months post-treatment.

The Meat Research Corporation (MRC) has been consulted on overseas trade aspects relating to residues in food. To ensure residue surveillance programs in importing countries do not detect residues of dicyclanil, the MRC has proposed an export slaughter interval (ESI) of 120 days.

The Australian label will direct users to check overseas standards where dicyclanil-treated sheep are to be slaughtered for export.

Novartis intends to seek registration in Europe and South Africa. Registration and the concurrent establishment of MRLs will ease trade concerns in these regions.

## Occupational Health and Safety Assessment

Dicyclanil is not listed as a hazardous substance in the draft National Occupational Health and Safety Commission (NOHSC) *List of Designated Hazardous Substances*. Novartis Animal Health Australasia Limited (Novartis) has determined dicyclanil to be a hazardous substance according to NOHSC criteria, based on acute oral and inhalation toxicity. The Following risk and safety phrases are allocated to dicyclanil:

| | |
|---|---|
| R22 | Harmful if swallowed |
| R20 | Harmful by inhalation |
| S2 | Keep out of reach of children |
| S13 | Keep away from food, drink, and animal feeding stuffs |
| S22 | Do not breathe dust |
| S36/37/39 | Wear suitable protective clothing, gloves and eye/face protection |
| S46 | If swallowed, contact a doctor or Poisons Information Centre immediately and show this container or label |

Substances containing dicyclanil are hazardous when it is present at concentrations =25%. Dicyclanil is a fine white powder. In experimental animals (rats), Dicyclanil had moderate acute oral ($LD_{50}$ was 560 mg/kg, males) and low acute dermal ($LD_{50}$ >2000 mg/kg) and inhalation ($LC_{50}$ 3184 mg/kg) toxicity. It was slight skin and eye irritant in rabbits. It did not induce sensitisation by topical contact in guinea pigs, although intradermal repeated dosing caused an allergic reaction in the same species.

The acute toxicity, irritancy and dermal sensitisation properties of Spray-On Sheep Blowfly Treatment (CLIK®) have not been investigated. However, a similar formulation (5% dicyclanil) has low oral and dermal toxicity (oral and dermal $LD_{50}$ >5000 mg/kg, no deaths) in rats, is a slight skin and eye irritant in rabbits and is not a skin sensitiser in guinea pigs.

***Formulation, transport, storage and retailing***

The product will be formulated in Australia from imported technical grade active constituent (TGAC). Dicyclanil technical (powder) is packaged in 20-kg quantities in a polyethylene bag inside a steel drum. CLIK® will be sold in 5 L and 20 L packs. The 5-L pack will be in HDPE bottles and the 20-L quantity will be packed in HDPE drums. Laboratory staff (testing the TGAC), formulators and packers could be exposed to the TGAC and the product. Transport, storage and retail workers will also handle the product but could only be exposed to the product if packaging is breached.

Advice on the safe handling of the product is provided in the Material Safety Data Sheet (MSDS) of the product.

*End use*
CLIK® is indicated for protection of sheep, both off-shears and long wool, against fly strike. It is applied as a low-volume spray treatment onto or near areas where protection is required. The product is to be used undiluted, directly from the container using a spray-on applicator gun recommended by Novartis. The dose volume is determined by the weight of sheep being treated. The recommended dose volume is <0.7-2 mL product/ kg live weight to achieve a dose rate of <35-100 mg dicyclanil/kg live weight. This dosage is expected to protect sheep against fly strike for 18 to 24 weeks after treatment.

CLIK® is not to be applied less than 28 days before slaughter for human consumption and less than two months before shearing. It is not to be used on sheep which are producing or may in future produce milk or milk products for human consumption.

No worker exposure data was available to assess the risks of long term use of Dicyclanil. Given the controlled mechanisms for using the product, it is considered safe to use in the short or long term.

*Handling of treated animals*
Animals may need to be herded soon after treatment for sale or other purposes, but this should not involve close human contact with the treated area. Occasionally, individual treated animals may require close handling. There are no occupational health and safety concerns for workers handling treated animals.

A theoretical calculation for wool residue exposure to shearers was carried out for risk assessment. The results indicated that residues of dicyclanil in the lamb fleece are not of concern during shearing because dissipation data for lamb fleeces indicate that shearers could absorb dicyclanil residues of 0.0073 mg/kg bw/day. The risk assessment indicates that elbow-length rubber gloves are required when opening the container and using the product.

*Recommendations for safe use*
End users should follow the instructions and Safety Directions on the product labels. Safety Directions include the use of personal protective equipment (PPE), namely elbow-length rubber gloves when opening the container and using the product.

The PPE recommended should meet the relevant Standards Australia standard specified below:

> AS 2161-1978 Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)

Novartis Animal Health Australasia Limited has produced a MSDS for CLIK® Spray-On Sheep Treatment. This should contain information relevant to Australian workers, as outlined in the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets.* Employers should obtain the MSDS from the supplier and ensure that their employees have ready access to it.

*Conclusions*
CLIK® Spray-On Sheep Treatment can be used safely if handled in accordance with the instructions on the product labels. Additional information is available on the product MSDS.

# Environmental Assessment

Novartis Animal Health Australasia Pty Ltd has applied for registration of the new product CLIK® SPRAY-ON Sheep Blowfly Treatment, containing the new active ingredient dicyclanil (50 $g.L^{-1}$ "suspo-emulsion" formulation), for control of blowfly (*Lucilia cuprina*) strike in sheep. Dicyclanil is an ectoparasiticide, its mode of action being as an insect growth regulator, preventing fly larvae from developing into pupae or adults. It has some similarity in molecular structure to cyromazine, an insect growth regulator already in use for veterinary and plant purposes.

**Environmental fate**

***Hydrolysis***

A hydrolysis study with radiolabelled dicyclanil was reported, with incubation in the dark under generally sterile conditions at pH 1, 3, 5, 7, 9 and 13 at ~50°C for 14 days. The studies showed that except under very alkaline conditions (pH 13), dicyclanil was hydrolytically stable, with a calculated hydrolysis half-life in excess of 1 year at 20-40°C.

***Photolysis***

A study of the photodegradation of dicyclanil in water (~10 ppm in pH 7 buffer) was conducted using cyclic illumination (12 hour light/12 hour dark) with an artificial light source (filtered Xenon arc lamp). Little degradation occurred in dark control samples (half-life = 144 days) and degradation was also slow in irradiated samples under non-sensitised conditions (half-life = 61.2 days), but photodegradation occurred relatively rapidly in the presence of sensitisers (half-life 2.5 days with 1% acetone and 5.1 days with 10 ppm humic acids).

The study indicated that under aqueous conditions dicyclanil is only slightly photodegradable ($DT_{50}$ > 720 hours continuous illumination) in the absence of sensitisers, but fairly to readily photodegradable ($DT_{50}$ = 96-240 or 24-96 hours continuous illumination, respectively) in the presence of sensitisers such as acetone or naturally occurring humic acids. The main photoproduct was the dealkylation metabolite CGA 297107 (peak concentration 25-46% of applied radioactivity), with CGA 297106, produced by hydrolysis of CGA 297107, also present at up to 9% of applied radioactivity in the acetone study.

***Degradation in soil and water***

**Aerobic soil metabolism.** A study was provided of the degradation of $^{14}$C-dicyclanil (labelled at the 2-pyrimidine position) in a loam soil under moist (75% of field capacity), aerobic conditions at ~20°C, with incubation continuing for up to 273 days. Dicyclanil was found to degrade rapidly, predominantly by dealkylation (loss of the cyclopropane ring) to form the metabolite CGA 297107 (peak concentration ~78% of applied radioactivity on the seventh day of incubation, declining to ~28% of applied radioactivity at the end of the incubation period). Calculated half-lives for dicyclanil and CGA 297107 in the study were ~1.5 days and ~157-173 days, respectively.

A second identified metabolite was dicyclanil hydroxylated in the cyclopropane ring (peak concentration on day 21 of incubation at ~4-5% of applied radioactivity), and various other unidentified metabolites were detected at lower peak concentrations. Non-extractable radioactivity increased over the first 168 days of incubation to a peak of ~38% of applied radioactivity, before falling slightly to ~35% of applied radioactivity at 273 days. Cumulative evolution of $^{14}$C-carbon dioxide at the end of the study had reached 24% of applied radioactivity, indicating significant mineralisation of the dicyclanil molecule. Thus dicyclanil

is readily degradable (DT50 < 20 days) in soil under moist, aerobic conditions, but the principal metabolite formed, CGA 297107, is only slightly degradable (DT50 in the range 60-180 days) under the same conditions.

**Ready biodegradability.** A $CO_2$ evolution test found that none of the theoretical C content of dicyclanil was evolved over a 29 day incubation period at 22°C, indicating the substance is classified as "not readily biodegradable" according to this standard test with activated sludge.

***Mobility***

Dicyclanil is very slightly volatile [vapour pressure < 1 x $10^{-3}$ Pa, H (Henry's Law Constant) < 1 x $10^{-5}$] and unlikely to evaporate significantly from soil or water. A batch equilibrium study of adsorption and desorption of dicyclanil on 5 soils indicated $K_{OC}$ values for adsorption ranging from 89 to 273 (average 136) and desorption ranging from 108 to 403 (mean 186) for the first desorption cycle and 131 to 667 (mean 286) for the second desorption cycle. These data indicate that dicyclanil is likely to have medium to high mobility in soil ($K_{OC}$ in the range 150-500 or 50-150, respectively). The results are consistent with the moderate water solubility (= 350 mg.$L^{-1}$) and lack of lipophilicity of the substance (indicated by its log $K_{OW}$ value of 0.51-0.69).

Some mobility in soil of dicyclanil and its metabolites was indicated in an aged soil leaching study, where a loam soil was incubated with $^{14}$C-labelled dicyclanil for 73 hours and applied to columns of the same loam soil or a loamy sand soil, followed by leaching with the equivalent of 200 mm water over = 48 hours. The aged soil contained 19.3% of applied radioactivity as dicyclanil, 70.0% as CGA 297107, 2.1% of applied radioactivity as U7.2, plus small amounts of various unknown metabolites. After leaching, the applied residues were largely restricted to the top 14-cm of the soil column with the loamy sand and the top 20-cm with the loam, with similar downward movement of dicyclanil and the principal metabolite CGA 297107. Very little radioactivity (< 0.2% of applied radioactivity) was present in the leachate.

Calculations by Environment Australia of the Gustafson Ubiquity Score (GUS) using the available $K_{OC}$ and half-life data indicate that dicyclanil is an "improbable leacher" (GUS < 1.8), whereas assuming it has a similar $K_{OC}$ to dicyclanil, CGA 297107 is a "probable leacher" (GUS > 2.8). These results reflect the short and long half-life, respectively, of these substances.

***Field dissipation***

A field dissipation study with dicyclanil was not provided, but the laboratory aerobic soil metabolism study indicates that dicyclanil reaching soil should degrade rapidly, largely to the metabolite CGA 297107, which should degrade more slowly. Some downward movement of the parent compound and metabolites may occur. No accumulation of dicyclanil in soil is expected.

***Bioaccumulation***

Based on its octanol/water partition coefficient (log $K_{OW}$ = 0.51-0.69), dicyclanil is unlikely to bioconcentrate in fish, and has a predicted bioconcentration factor of ~2.

***Fate of substance applied to sheep***

**Fate in the period immediately following application.** Two studies have examined the fate of dicyclanil in the period immediately following application to sheep by either a pour-on method (using a formulation similar, but not identical, to CLIK® ) or jetting (using a different formulation). Retention of the applied spray was 90.0-98.2% (mean 94.7%) of the applied amount with the pour-on, but only 39-59% (mean 49.4%) with jetting (where the main loss

was to run-off - mean 37% of the dose to be administered). The data suggested that a small amount of the dried dose was lost by rub-off in the first 7 days after application (= 3.9% with pour-on application and = 1.4% with jetting). Absorption was estimated at 4% of the applied dose with pour-on application and 2% of the retained dose with jetting, most of the absorbed dose being recovered in urine and faeces. Residues in fleece were concentrated in the area where the substance was applied, but with low levels in untreated areas, indicating some spread of the material within the fleece.

**Fate in wool between application and shearing**. Three studies examined the fate of dicyclanil in wool, two studies with pour-on application (monitored for 20 and 46 weeks, respectively) and one with jetting (monitored for 24 weeks), again with different formulations for pour-on and jetting. Sheep were kept dry or exposed to simulated rain treatments, in both cases being kept under cover (hence significant photodegradation of dicyclanil is unlikely to have occurred, whereas this may be a possibility in practice). The concentration of dicyclanil remaining in wool was potentially affected by growth dilution (increase in staple length) as well as dissipation by degradation, absorption and movement within and from the fleece.

In the 20-week pour-on study, mean residues in whole staples from the treated backline area of sheep kept dry or exposed to a rain treatment declined from 10.9 $g.kg^{-1}$ and 13.7 $g.kg^{-1}$, respectively, one week after application to 1.45 $g.kg^{-1}$ and < 0.04 $g.kg^{-1}$, respectively, after 20 weeks (half-lives calculated by Environment Australia 53.2 and 6.5 days, respectively, in sheep kept dry or exposed to 500 mm rain). In the 46 week pour-on study, mean residues in whole staples from the treated backline area of sheep kept dry or exposed to a rain treatment declined from 8.58 $g.kg^{-1}$ and 4.92 $g.kg^{-1}$, respectively, 2 weeks after application to 1.88 $g.kg^{-1}$ and 0.026 $g.kg^{-1}$, respectively, after 23 weeks, and were 0.37 $g.kg^{-1}$ after 46 weeks in sheep kept dry (half-lives calculated by Environment Australia 70.7 and 19.9 days, respectively, in sheep kept dry or exposed to 1000 mm rain).

In both studies, mean whole staple residues in wool from the flanks, which had not been directly treated, were much lower (0.37-0.39 $g.kg^{-1}$ at one week in the 20 week study and 0.29-0.34 $g.kg^{-1}$ in the 46 week study, falling to = 0.10 $g.kg^{-1}$ by 20-23 weeks - half-lives calculated by Environment Australia for sheep kept dry were 68.4 and 22.1 days, respectively, in the 20 week and 46 week study). In the jetting study, mean residues in whole staples from the treated area of sheep were much lower, falling from 0.94-1.80 $g.kg^{-1}$ 2 days after application to 0.20-0.33 $g.kg^{-1}$ after 24 weeks, final residues with a rain treatment differing little from those in sheep kept dry, despite more rapid initial dissipation (half-lives calculated by Environment Australia = 67.4-82.6 days).

Environment Australia notes that none of these sheep were regularly exposed to sunlight, and the rate of degradation is potentially faster where there is opportunity for photodegradation to occur. Nonetheless, depending on the interval between application and shearing and the amount of exposure of the sheep to rain, a significant proportion of the applied substance may remain in wool at shearing, albeit at lower concentrations due to growth dilution as well as other means of dissipation.

In all cases, dicyclanil residues were largely concentrated in the portion of the staple which had originally been treated (i.e. the tip). Residues of the metabolite CGA 297107 were measured in the pour-on studies and found to be present at only low peak concentrations (mean whole staple concentration in backline wool < 0.10 $g.kg^{-1}$).

*Fate in wool during scouring*

The fate of dicyclanil and the metabolite CGA 297107 in wool during the scouring process was examined using wool from merino sheep which had been treated with the same formulation as used for the above pour-on studies (similar, but not identical to that proposed for CLIK®) at a dose rate of 35 mL (1.75 g ai) per sheep 38 days after shearing. The sheep had been shorn 88 days later, during which they were exposed to sunlight and 169 mm of rain. The baled wool was found to contain 107 mg dicyclanil and 66.3 mg CGA 297107 per kg wool (ie. lower dicyclanil residues than expected and much more of the metabolite than encountered in the other wool studies). Based on the measured residues of dicyclanil and a wool growth model, a dicyclanil half-life of 30 days was estimated under these conditions.

The lot of wool was put through a pilot scale wool scouring process, in which it was found that the dicyclanil and CGA 297107 were associated with the aqueous discharges from scouring and there was little association with the wool, wool wax or dirt fractions. It was also confirmed that both substances were poorly removed by on-site effluent treatment systems designed principally to remove wool wax. Thus most dicyclanil and CGA 297107 residues in wool are likely to reach sewage effluent as a result of the scouring process and the small proportion of residues remaining in clean wool are expected to be removed in subsequent treatment, such as dyeing.

**Environmental toxicity**

*Birds*

A study of the acute oral toxicity of dicyclanil TGAC indicate that the $LD_{50}$ from a single oral dose was in the range 500-1620 mg ai.$kg^{-1}$ bodyweight to Japanese quail (*Coturnix coturnix japonica*), indicating that the substance is slightly toxic to this bird species ($LD_{50}$ > 500, = 2000 mg.$kg^{-1}$ bw). The NOEL for this test was much lower than the $LD_{50}$, at 50 mg.$kg^{-1}$ bw, because while mortalities occurred only at the highest dose (1620 mg ai.$kg^{-1}$), various other (usually temporary) effects were observed at lower doses (lethargy at 50-1620 mg ai.$kg^{-1}$, lower food consumption for a period at 154-1620 mg ai.$kg^{-1}$ and more serious effects at 500 and 1620 mg ai.$kg^{-1}$). A subacute dietary toxicity study with dicyclanil and the same species indicated an $LC_{50}$ with dicyclanil of > 5000 ppm, ie. practically non-toxic. Based on a very minor effect of dicyclanil on initial food consumption at 490 ppm, the NOEL was < 490, with more practically significant effects on food consumption and bodyweight gain evident at 1565 ppm.

*Aquatic organisms*

**Fish.** Acute toxicity tests (96 hour exposure, static test conditions) with dicyclanil indicated an $LC_{50}$ value in the range 32-68.3 mg.$L^{-1}$ (nominal concentrations; NOEC = 32 mg.$L^{-1}$) to rainbow trout (*Onchorynchus mykiss*) and an $LC_{50}$ of > 67.8 mg.$L^{-1}$ (mean measured concentrations; NOEC = 37.8 mg.$L^{-1}$) to bluegill sunfish (*Lepomis macrochirus*). A limit test of the toxicity of the metabolite CGA 297107 to rainbow trout indicated an $LC_{50}$ > 86.5 mg.$L^{-1}$ and NOEC < 86.5 mg.$L^{-1}$. Hence both substances are at most slightly toxic (10 < $LC_{50}$ = 100 mg.$L^{-1}$) to these fish species.

*Aquatic invertebrates*

Acute toxicity tests (24 or 48 hours exposure under static test conditions) with dicyclanil and the daphnid *Daphnia magna* indicated that with acute exposure, dicyclanil was moderately toxic to daphnids (24 hour $EC_{50}$ = 17 mg.$L^{-1}$ nominal concentration in one test, 48 hour EC50 = 8.3 mg.$L^{-1}$ nominal concentration in a second test and 48 hour EC50 = 1.1 mg.$L^{-1}$ in a third test with measured concentrations). In each case, the NOEC was much lower than the EC50

for immobilisation (0.58 $mg.L^{-1}$, < 0.58 $mg.L^{-1}$ and 0.08 $mg.L^{-1}$, respectively). An acute toxicity test with the metabolite CGA 297107 and *D. magna* indicated a 48 hour EC50 of > 100 $mg.L^{-1}$ (NOEC = 100 $mg.L^{-1}$), ie. practically non-toxic.

A test of the chronic exposure (21 days) and reproductive toxicity of dicyclanil indicated greater toxicity to adult daphnids (21 day $EC_{50}$ in the range 0.060-0.19 $mg.L^{-1}$ nominal concentrations) and much greater toxicity to reproduction ($EC_{50}$ could not be calculated, but the NOEC was < 0.0019 $mg.L^{-1}$ based on statistical comparison with the control, though the practical effect of this difference appeared minor). Measured concentration data were not obtained in this test and Environment Australia judged the test deficient. However, it will be used for hazard assessment, as chronic/reproductive toxicity to daphnids appears to be the most sensitive aquatic toxicity indicator and no other suitable tests are available.

***Diatoms, algae and aquatic plants***
72-hour growth inhibition tests indicate that dicyclanil and the metabolite CGA 297107 are both slightly toxic to freshwater green algae ($EbC_{50}$ of dicyclanil to *Scenedesmus subspicatus* = 19.5 $mg.L^{-1}$ and $EbC_{50}$ of CGA 297107 to *Selenastrum capricornutum* = 74.8 $mg.L^{-1}$, both based on mean measured concentrations).

***Terrestrial invertebrates***
Two studies of the toxicity of dicyclanil to the earthworm species *Eisenia foetida foetida* were reported, one indicating a 14 day exposure $LC_{50}$ > 1000 $mg.kg^{-1}$ dry soil (NOEC < 62.5 $mg.kg^{-1}$), and the other a 14 day $LC_{50}$ of 510 $mg.kg^{-1}$ (NOEC = 37 $mg.kg^{-1}$ - all nominal concentrations). Thus dicyclanil is slightly toxic to earthworms exposed to it in soil ($LC_{50}$ in the range 100-1000 mg $ai.kg^{-1}$ dry soil).

***Phytotoxicity***
Phytotoxicity from dicyclanil appears unlikely following use of the substance directly on sheep.

***Micro-organisms***
An activated sludge respiration inhibition test indicated no significant inhibitory effect of dicyclanil in the concentration range tested (up to 105.5 $mg.L^{-1}$), thus dicyclanil has low toxicity to sludge microorganisms. This result is consistent with results of a test with the reference substance in the Ready Biodegradability Test discussed earlier.

**Environmental hazard**

***Hazard to birds***
Dicyclanil is applied topically to sheep and exposure to birds is expected to be insignificant. Furthermore, the substance has low toxicity to birds with either acute or chronic exposure. Hence dicyclanil used in accordance with label recommendations is not likely to present a hazard to birds.

***Hazard to aquatic organisms, terrestrial invertebrates and plants***
**Residues reaching soil and water on grazing properties.** The applicant presented a hazard analysis based on a worst case situation of 20% of an applied dose of 1.75 g $ai.head^{-1}$ reaching soil (due to losses during application and/or by elimination from the animal following absorption and/or by rub-off of dried spray), with a stocking rate of 15 $sheep.ha^{-1}$ and assuming total transfer of this quantity without loss to the top 5 cm of soil (bulk density 1.5 $g.cm^{-3}$).

In this situation, 5250 mg $ai.ha^{-1}$ would be transferred to soil, resulting in a peak concentration of 7 µg $ai.kg^{-1}$ soil, which would be expected to decline below 1 $\mu g.kg^{-1}$ within approximately

one week (aerobic soil degradation half-life ~ 1.5 days). Environment Australia notes that even if these residues were 100 x higher (700 $\mu g.kg^{-1}$) due to higher short term stocking rates, soil residues would still be well below the 14 day NOEC for earthworms (37 mg $ai.kg^{-1}$ soil) and would not be expected to cause phytotoxicity (greenhouse tests not seen by Environment Australia indicated no effects of rates up to 1 $kg.ha^{-1}$). Rapid degradation to the metabolite CGA 297107 should prevent soil accumulation or leaching of the parent substance. This metabolite would be expected to degrade much more slowly, but seems less toxic and should mineralise slowly and/or form residues bound to soil.

As the substance is applied topically to sheep, Environment Australia believes that contamination of aquatic areas on farms is unlikely, but that it is possible, e.g. if heavy rainfall followed shortly after application while sheep were still gathered near the treatment area. In a worst case situation where it is assumed that 1% of the dose applied to 100 sheep (1.75 g $ai.head^{-1}$) washed off per 1 ML water (eg. 2 cm rain over 5 ha), the resulting concentration in the water would be 17.5 $\mu g.L^{-1}$ with no further dilution. This is below the acute exposure $EC_{50}$ or NOEC to *Daphnia magna*, (1.1 and 0.08 $mg.L^{-1}$, respectively) but exceeds the chronic exposure NOEC to this species (1 $\mu g.L^{-1}$). However, chronic exposure is not expected on grazing properties, as the substance is applied only once per year, further dilution would be expected to occur and dicyclanil is susceptible to photodegradation in water containing humic acids (half-life in the absence of turbidity = 5.1 estimated summer days). Hence little toxicity to aquatic organisms is expected to occur on farms where the product is used, but Environment Australia notes and supports the label comment which forbids contamination of dams, rivers or streams with the product or used containers.

**Residues reaching the environment from scouring of treated wool.** Environment Australia assumes that the majority of residues from dicyclanil applied to sheep will degrade in the fleece between application and shearing, or remain in the fleece and be removed during scouring. The applicant presented evidence of half-lives for dicyclanil in wool on the sheep ranging from ~30 days (based on residues in a wool scouring study, where sheep were exposed to sunlight and 169 mm of rain over a 12 week period between application and shearing) to ~140 days (in sheep protected from sunlight and rain). The applicant maintains that the great majority of use of the product will be off-shears to 6 weeks after shearing.

Hence Environment Australia determined predicted environmental concentrations of dicyclanil based on a range of scenarios as follows, with 30, 70 and 140 day half-lives:

1) 75% of the product used going to wool which is shorn at 40 weeks after application (12 weeks off shears) + 25% going to wool shorn at 8 weeks after application;
2) 75% of the product used going to wool which is shorn at 40 weeks after application (12 weeks off shears) + 25% going to wool shorn at 12 weeks after application;
3) 90% of the product used going to wool which is shorn at 40 weeks after application (12 weeks off shears) + 10% going to wool shorn at 8 weeks after application;
4) 90% of the product used going to wool which is shorn at 40 weeks after application (12 weeks off shears) + 10% going to wool shorn at 12 weeks after application;
5) 90% of the product used going to wool which is shorn at 40 weeks after application (12 weeks off shears) + 10% going to wool shorn at 16 weeks after application.

A residue concentration of 100 mg $ai.kg^{-1}$ wool was also used, as in some hazard assessments provided by the applicant.

***Wool scour effluent and Sewerage Acceptance Guidelines***

An assessment provided by the applicant indicated that the maximum discharge level of 1 $mg.L^{-1}$ for an individual pesticide recommended under the National Water Quality Management Strategy will be reached by an average dicyclanil residue of 10 $mg.kg^{-1}$ in wool to be processed with water consumption of 10 $L.kg^{-1}$ wool. Based on a range of market share, this guideline would be met under all the above scenarios with half-lives of 30-70 days (predicted concentrations of dicyclanil in wool scour effluent would be 0.03-0.34 $mg.L^{-1}$ with a 30 day half-life and 0.29-0.94 $mg.L^{-1}$ with a 70 day half-life).

***Ocean discharge in Australia***

Assuming the Geelong Black Rock ocean outfall treatment plant to be a worst case for ocean discharge in Australia, on average, effluent arriving from scouring of 50 tonnes wool per day would be diluted in a daily flow of 50 ML. Thus wool scour effluent with a concentration of 1 $mg.L^{-1}$ (as from wool containing an average of 10 mg dicyclanil.$kg^{-1}$) would be diluted to 10 $\mu g.L^{-1}$ in the effluent leaving the sewerage plant. This concentration (hence again all the above scenarios with half-life 30-70 days) falls below the acute exposure NOEC for daphnids and is further diluted as the effluent reaches the ocean environment (a conservative dilution factor of 150 X would reduce the concentration in the outfall effluent of 10 $\mu g.L^{-1}$ to 0.067 $\mu g.L^{-1}$ in the ocean plume). However, of the above scenarios, only a 30 day half-life together with Scenarios 3, 4 and 5 (or Scenarios 4 and 5 only, depending on the market share) result in predicted effluent concentrations below the chronic toxicity NOEC for daphnids (1 $\mu g.L^{-1}$).

Environment Australia notes that dicyclanil from wool scours would be continually released at the ocean outfall, but concludes that the chronic hazard to marine organisms is low once the effluent is diluted in ocean water, though localised impacts may occur in the immediate vicinity of the discharge. However, Environment Australia also notes that assuming wool scours affecting the Werribee sewerage treatment plant process ~500 tonnes of wool per day, with an average daily flow of ~500 ML, resulting in similar initial concentrations to those at the Black Rock outfall.

Effluent passing through the Werribee works has a long residence time and largely undergoes tertiary treatment, which should facilitate degradation of dicyclanil through photolysis and aerobic soil degradation (the situation with dicyclanil differs from that with most other ectoparasiticides because it partitions to water rather than wax and sludge). However, if residues were to reach ponds at Werribee where daphnids are currently harvested before significant degradation occurred, there may be harmful effects on the daphnid populations present due to chronic toxicity effects.

Environment Australia acknowledges that there appears to be little risk of harm occurring to organisms in the environment once effluent water leaves ocean outfalls and is sufficiently diluted in the outfall plume. However, to minimise the risk of localised impacts occurring near effluent outfalls or within the Werribee plant (in the absence of information to indicate this is not a hazard), Environment Australia recommends a 12 week shearing withholding period.

***River discharge in the UK***

The applicant provided an hazard assessment for a worst case situation of a processing centre processing 27.6 tonnes per day of mainly Australian wool and releasing effluent into a tributary of the Calder River in the UK (Spen Beck below Spedborough). Based on Environmental Quality Standards (EQSs) in the river water of 1 $\mu g.L^{-1}$ (as used by Environment Australia) and 0.2 $\mu g.L^{-1}$ (a more conservative figure allowing for possibly greater toxicity to aquatic Diptera), this assessment indicated appropriate maximum average concentrations of dicyclanil in Australian wool.

Environment Australia estimates that with a 30 day half-life, all 5 usage scenarios above would be acceptable under the 1 $\mu g.L^{-1}$ EQS with the maximum market share value used. With the more conservative EQS of 0.2 $\mu g.L^{-1}$, only Scenarios 3, 4 and 5 (or Scenarios 4 and 5, depending on the market share value used). With a 70 day half-life, Scenarios 2-5 (or Scenarios 3-5, depending on the market share value used) would be acceptable with the 1 $\mu g.L^{-1}$ EQS, but none of the Scenarios satisfies the guideline values for the more conservative 0.2 $\mu g.L^{-1}$ EQS.

While these are worst case estimates, they indicate the importance of half-life, market share and the extent of use within 2-3 months before shearing in determining whether the average amount of residues remaining in treated wool is acceptable. Environment Australia concludes that a shearing withholding period of at least 12 weeks should be applied to minimise the hazard to sensitive aquatic species arising in overseas rivers. Based on our analysis of Scenario 4, this would satisfy an EQS of 0.2 $\mu g.L^{-1}$, provided the half-life of dicyclanil in wool before shearing is of the order of 30 days (which Environment Australia accepts is reasonable with sunlight exposure and some rain, but believes may not be the case in relatively dry periods). The analysis provided by the applicant (based on a different usage model with a 30 day half-life) indicated that a longer half-life may be required to meet these trade considerations.

***Land-based disposal in Australia***

A worst case situation was considered for discharge of dicyclanil residues onto land, as occurs with inland scouring facilities in Australia. Assuming a throughput of 150 tonnes wool containing an average of 10 mg dicyclanil.$kg^{-1}$ per week and effluent production of 1.5 ML per week used to irrigate 100 ha (ignoring possible evaporation losses during ponding), this would result in an average application to soil of 15 $g.ha^{-1}.week^{-1}$ (ignoring possible photolysis in holding ponds), or a cumulative rate of 780 $g.year^{-1}$.

However, with an aerobic soil degradation half-life of ~1.5 days and DT 90 of 5 days, little accumulation of dicyclanil in soil is expected, though some accumulation of the metabolite CGA 297107 may occur while application continued to the same area (aerobic soil degradation half-life 157-173 days). Thus peak soil concentrations of dicyclanil are unlikely to exceed 0.02 $mg.kg^{-1}$ soil, even if only confined to the surface 5 cm. As discussed above in regard to residues on-farm, this is well below toxic levels to earthworms and unlikely to result in an aquatic hazard through run-off. Furthermore, dicyclanil residues in wool are likely to be lower than an average of 10 $mg.kg^{-1}$ under expected practical scenarios (above).

***Conclusions regarding the environmental hazard from residues reaching scour effluent***

Residues arising from ocean sewerage effluent discharge are unlikely to present an aquatic hazard once they are diluted, but residues under various usage scenarios are sufficiently high that a localised hazard may arise near the discharge point because dicyclanil concentrations in the undiluted effluent may exceed chronic toxicity NOECs.

Depending on the rate of degradation of residues in effluent moving through the Werribee sewerage treatment plant, there is also a possibility of residues in effluent reaching ponds containing daphnids, where impacts due to chronic toxicity could occur. Environment Australia would therefore wish to ensure usage shortly before shearing is minimised. Promotion of the product for use off-shears to 6 weeks after shearing, together with pricing recognising prolonged control, should assist in this regard.

However, due to uncertainties about the chronic toxicity endpoint for aquatic invertebrates and because of the possibility of an additional contribution from cyromazine to aquatic toxicity in the same environment, Environment Australia recommends that an additional

margin of safety be provided by a shearing withholding period of 12 weeks (ie. making Scenario 4 the worst case, assuming use in the months approaching shearing is = 10% of total use of the product).

Environment Australia concludes that, based on a 12 week shearing withholding period, disposal of scour effluent on land is unlikely to present a significant hazard arising to land or aquatic organisms.

Trade considerations are also relevant to deciding an appropriate shearing withholding period, as an assessment of the hazard arising from wool scour effluent in rivers based on a worst case situation in the UK indicates that mean residues in Australian wool need to be restricted to 1.1 $mg.kg^{-1}$ to meet an Environmental Quality Standard of 0.2 $\mu g.L^{-1}$ in river water. Environment Australia agrees that a shearing withholding period of at least 12 weeks is necessary to meet this requirement at this EQS and notes that a loner withholding period may be specified because of these trade considerations.

***Conclusions***

Environment Australia has assessed data in support of CLIK® SPRAY-ON Sheep Blowfly Treatment and believes that the application contains adequate environmental fate and toxicity data to demonstrate that with the anticipated market share, the use of this product according to the label and good agricultural practice is unlikely to result in harmful effects on environmental organisms.

The greatest environmental hazard from use of the product is from exposure to aquatic invertebrates as a result of effluent from scouring of wool containing residues of dicyclanil. However, the aquatic hazard from this source should be acceptable with use predominantly off-shears to 8 weeks following shearing and with a shearing withholding period of 12 weeks.

## Assessment of Overseas Trade Aspects of Residues in Wool

*Commodities exported*
Data from the Australian Bureau of Statistics show that 58.6% of the Australian value of total exports of wool, for the year 95/96, was attributable to greasy wool, the major countries receiving the greasy wool being China Taiwan, Italy, France and Germany.

*Overseas registration status and environmental quality standards*
CLIK® Spray-On Sheep Blowfly Treatment is currently registered with a closely similar use pattern in New Zealand. Environmental quality standards for dicyclanil residues in wool have not been established in our major wool trading partners and can only be estimated.

*Australian environmental assessment*
Environment Australia has conducted a hazard assessment of residues in wool at shearing for CLIK® Spray-On Blowfly Treatment. The report concludes that the environmental hazard as a result of effluent from scouring of wool containing residues of dicyclanil is acceptable with use of the product predominantly off-shears to 8 weeks following shearing and with a shearing withholding period of 12 weeks.

*Potential risk to trade*
A discussion of trade considerations is included in the Environmental Assessment report conducted by Environment Australia. Based on a hazard assessment for a worst case situation of a processing centre processing mainly Australian wool and releasing effluent into a river tributary (River Aire/Calder in Leeds/Bradford, UK) Environment Australia concludes that a wool withholding period of at least 12 week should be applied to minimise the hazard to sensitive aquatic species arising in overseas rivers. For further details refer to the section 'Environmental Assessment'.

CSIRO Wool Technology has been consulted on overseas trade aspects relating to residues in wool. In the absence of environmental quality standards or industry statistics for Australia's major wool trading partners, CSIRO Wool Technology similarly based their hazard assessment on the UK model. They conclude that withholding periods required to meet environmental standards depend on the environmental quality standard values that may be established. They also conclude that based on the data provided CLIK® Spray-On Sheep Blowfly Treatment may be applied to sheep with up to 10.5 months of wool (if the EQS is established at 1 µg/L) or up to 8 months (if the EQS is established at 0.2µg/L).

The NRA recommends, based on use of the product according to label directions and Good Agricultural Practice and the applicant's predicted market share of the product,.that a 12-week withholding period will minimise any hazard to the environment in places outside Australia.

## Efficacy and Safety Assessment

Scientific experts from the State's Department of Agriculture/Primary Industries assessed the submitted scientific studies and found them to be sufficient to support the proposed label claims for the product.

Data submitted demonstrated that CLIK® Spray-on Sheep Blowfly Treatment:

- is efficacious against the target parasite (*Lucilia cuprina*);
- is efficacious against larvae when implanted into the fleece;
- prevents the establishment of strike under controlled conditions;
- prevents the establishment of strike under field conditions;
- is well tolerated by sheep and has a high margin of safety; and
- does not affect wool quality.

Dicylanil is an insect growth regulator (IGR) effectively preventing egg hatching and lethal against early stage diptera larvae (1$^{st}$ and 2$^{nd}$ instar). Efficacy of dicyclanil against *Lucilia cuprina* was established in two *in vitro* studies and a series of *in vivo* studies including three larval implant trails and three exposure house trials.

Efficacy of dicyclanil in the product CLIK® Spray-on Sheep Blowfly Treatment was further confirmed in the field with extensive field trials in Australia over three consecutive years and comprised:

- dose determination studies covering 12,512 lambs at 22 trial sites in the first year;
- dose confirmation studies covering 10,286 sheep at 19 trial sites in the second year; and
- dose confirmation studies covering 10,253 sheep (>6 weeks off-shears) at 16 trial sites and 3,942 sheep (off-shears) at 5 sites in the third year.

No adverse effects were recorded in any of the clinical field trials. In addition a detailed safety study was presented which showed that the product applied up to ten times the recommended dose had no adverse systemic effect or effect to the skin. A further study demonstrated that the product when used according to the label directions had no deleterious effects on leather quality.

**Labelling Requirements**

READY SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

# CLIK® SPRAY-ON
# SHEEP BLOWFLY TREATMENT

Active Constituent: **50 g/L DICYCLANIL**

For the protection of sheep, either off-shears or with any length wool, against fly strike (*Lucilia cuprina*) for 18 to 24 weeks

5 LITRES / 20 LITRES

**READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT**

**Novartis Animal Health Australasia Pty Limited, ACN 076 745 198,**
140-150 Bungaree Road, Pendle Hill NSW 2145



**NOVARTIS LOGO**

DIRECTIONS FOR USE

Restraints –

**1. DO NOT use on sheep which are producing or may in the future produce milk or milk products for human consumption.**

**2. DO NOT use on open wounds, e.g. those resulting from marking or mulesing operations.**

**3. DO NOT dilute.**

**4. DO NOT mix with any other product.**

**5. DO NOT apply during gusty or windy weather as spray drift will reduce the period of protection.**

| FOR THE PREVENTION OF BODY STRIKE | | | | | | Critical Comments |
|---|---|---|---|---|---|---|
| SHEEP WEIGHT (kg) | TOTAL VOLUME/ SHEEP (mL) | VOLUME PER TREATMENT BAND (nearest mL) | NO. OF BANDS | NO. OF SHEEP TREATED PER 5 L | 20 L | 1. Use only a spray-on applicator gun recommended by Novartis.<br>2. Ensure the applicator gun is clean.<br>3. Calibrate applicator gun using an accurate volume measure. |
| 10 -20 | 14 | 7 | 2 | 357 | 1428 | 4. Ensure all areas to be protected are treated. |
| 21 - 30 | 16 | 8 | 2 | 312 | 1250 | 5. When preventing body strike ensure bands overlap along the midline - see diagram: |
| 31 - 50 | 20 | 10 | 2 | 250 | 1000 | |
| > 50 | 24 | 12 | 2 | 208 | 833 | |
| FOR THE PREVENTION OF BODY AND CRUTCH STRIKE | | | | | | |
| SHEEP WEIGHT (kg) | TOTAL VOLUME/ SHEEP (mL) | VOLUME PER TREATMENT BAND (nearest mL) | NO. OF BANDS | NO. OF SHEEP TREATED PER 5 L | 20 L | [PICTOGRAM OF SPRAY APPLICATION TO SHEEP] |
| 10 - 20 | 20 | 7 | 3 | 250 | 1000 | 6. This product is not recommended for treating existing strikes. Use a product such as Topclip® Blue Shield as a dressing for existing strikes.<br>7. Heavy rain following the application of this product could diminish the period of protection.<br>8.Clik Spray-On contains a scourable colouring agent for easy band identification. |
| 21 - 30 | 25 | 8 | 3 | 200 | 800 | |
| 31 - 50 | 30 | 10 | 3 | 166 | 666 | |
| > 50 | 35 | 12 | 3 | 142 | 571 | |

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

**WITHHOLDING PERIODS:**

**MEAT: DO NOT USE LESS THAN 28 DAYS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION.**

**MILK: DO NOT USE ON SHEEP WHICH ARE PRODUCING OR MAY IN THE FUTURE PRODUCE MILK OR MILK PRODUCTS FOR HUMAN CONSUMPTION.**

WOOL: DO NOT USE LESS THAN 3 MONTHS BEFORE SHEARING.

**Note: The withholding period for meat applies only to meat destined for the Australian domestic market. Some export markets apply different standards which may require an export slaughter interval. If meat from the animal on which this product is to be used may be sold outside the Australian domestic market, details of overseas standards should be obtained prior to use of this product.**

## GENERAL INSTRUCTIONS

CLIK Spray-on provides season length protection to sheep against fly strike and may be used either off-shears or on sheep with any length wool.
The dose volume is determined by the weight of sheep being treated. Apply CLIK Spray-On according to the diagrams and tables in the Directions for Use.
**DO NOT DILUTE**. Apply directly from the container using a spray-on applicator gun recommended by Novartis.
CLIK Spray-On may be applied to all breeds of sheep to obtain protection against fly strike.
CLIK Spray-On is applied as a low-volume treatment onto or near areas where protection is required. When applying, the nozzle of **the applicator gun should be approximately 25cm above the fleece,** to achieve a 15cm wide band at each pass.
Reduced efficacy may occur in sheep affected with dermatophilosis.

## SAFETY DIRECTIONS

**May irritate the eyes and skin. Avoid contact with eyes and skin. When opening the container and using the product wear elbow-length rubber gloves. Wash hands after use.**

## FIRST AID

**If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126) .**

### Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, rivers or streams with the product or used containers.

### Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

### Storage

Keep out of reach of children. Store below 30°C (Room Temperature). Protect from frost. Store in original container tightly closed in a dry, cool place. Do not store in direct sunlight. Do not re-use the container.

| | |
|---|---|
| **Batch Number:** | |
| **Expiry Date:** | |

### Disposal

Triple or (preferably) pressure rinse container and dispose of rinsate in disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and roots. Do not dispose of undiluted chemicals on-site. Break, crush or puncture and bury empty containers in a local authority landfill. If not available bury the containers below 500mm in disposal pit as for rinsate. Empty containers and product should not be burnt.

MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY

**This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations for liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.**

NRA 50005/0998

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia
8.30 am to 5.00 pm E.S.T. Monday to Friday

## Glossary

| | |
|---|---|
| **Active constituent** | The substance that is primarily responsible for the effect produced by a chemical product. |
| **Acceptable daily intake** | The daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer on the basis of all the known facts at the time. |
| **Acute** | Having rapid onset and of short duration. |
| **Carcinogenicity** | The ability to cause cancer. |
| **Chronic** | Of long duration. |
| **Codex MRL** | Internationally published standard maximum residue limit. |
| **Desorption** | Removal of an absorbed material from a surface. |
| **Ectoparasiticide** | A veterinary chemical product that is administered or applied to an animal by any means for the control, treatment or prevention of infestations with arthropod parasites. |
| **Efficacy** | Production of the desired effect. |
| **Formulation** | A combination of both active and inactive constituents to form the end use product. |
| **Good agricultural practice** | The nationally recommended, authorised or registered use-pattern of chemicals that is necessary for effective and reliable pest control under actual conditions at any stage of production storage, transport, distribution and processing of food commodities and animal feed. |
| **Genotoxicity** | The ability to damage genetic material |
| **Hydrophobic** | Water repelling |
| **$LC_{50}$** | The concentration of a substance in air that produces death by inhalation in 50 per cent of a population of experimental organisms. |
| **$LD_{50}$** | The dose of a substance that produces death in 50 per cent of a population of experimental organisms. |
| **Leaching** | Removal of a compound by use of a solvent. |
| **Log $P_{ow}$** | Log to base 10 of octonol water partitioning co-efficient. |

| | |
|---|---|
| **Limit of quantitation** | The level below which an analytical method is unable to accurately quantify the substance being measured. |
| **Material safety data sheet** | Data sheets produced by manufacturers/importers which provide the information needed to allow the safe handling of hazardous substances used at work. |
| **Maximum residue limit** | The maximum concentration of a chemical residue that is legally permitted in or on a food or food commodity when that chemical is applied according to good agricultural practice or good practice in the use of veterinary drugs. |
| **Metabolism** | The conversion of food into energy |
| **No observable effect level** | The highest concentration or amount of a substance, found by study or observation, to cause no detectable (usually adverse) alteration of morphology, functional capacity, growth, development or life span of the most sensitive organism |
| **Photodegradation** | Breakdown of chemicals due to the action of light. |
| **Photolysis** | Breakdown of chemicals due to the action of light. |
| **Residue** | The remains of the active constituent(s) in a chemical product persisting in or on food, agricultural commodities or plants, soil, water or other environmental components, together with all derivatives, metabolites, and degradation products of the active constituent(s) arising from their use. |
| **Technical grade active constituent** | The commercial grade of an active constituent as it comes from the manufacturing plant and before it has been formulated. |
| **Toxicokinetics** | The study of the movement of toxins through the body. |
| **Toxicology** | The study of the nature and effects of poisons. |

## References

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