Australian Government

Australian Pesticides and Veterinary Medicines Authority

# FIPRONIL

# VOLUME 1

# PRELIMINARY REVIEW FINDINGS REPORT

The reconsideration of the active constituent fipronil, registration of products containing fipronil and approvals of their associated labels

**JUNE 2011**

This document is published by the APVMA. In referencing this document the APVMA should be cited as both author and publisher.

ISBN: 978-0-9870591-7-8

Website: This publication is available from the APVMA website: http://www.apvma.gov.au

Comments and enquiries may be directed to:

Manager Chemical Review
Australian Pesticides & Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604
Australia

Telephone: +61 2 6210 4700
Fax: +61 2 6210 4776
Email: chemicalreview@apvma.gov.au

# CONTENTS

# LIST OF TABLES

# FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*.

The APVMA can reconsider the approval of an active constituent, the registration of a chemical product or the approval of a label for a container for a chemical product at any time. This is outlined in Part 2, Division 4 of the Agvet Codes.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product containing that chemical, or its label.

The reconsideration process includes a call for information from a variety of sources, a review of that information and, following public consultation, a decision about the future use of the chemical or product. The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken.

In undertaking reconsiderations (hereafter referred to as reviews), the APVMA works in close cooperation with advisory agencies including the Office of Chemical Safety within the Department of Health and Ageing, the Department of the Environment and Water Resources, state departments of agriculture, and other expert advisers as appropriate.

The APVMA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. The publication of review reports is a part of that process.

The APVMA also makes these reports available to the regulatory agencies of other countries as part of bilateral agreements. The APVMA recommends that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

The basis for the current reconsideration is whether the APVMA is satisfied that continued use of the active constituent fipronil and products containing fipronil in accordance with the instructions for their use:

- would not be an undue hazard to the safety of people exposed to it during its handling; and
- would not be likely to have an effect that is harmful to human beings; and
- would not be likely to have an unintended effect that is harmful to animals.

The APVMA also considered whether product labels carry adequate instructions and warning statements.

This document sets out the preliminary review findings relating to fipronil-containing products (and their labels) intended for use in agricultural and veterinary situations; these have been nominated for review by the APVMA. The preliminary review findings and proposed recommendations are based on information collected from a variety of sources.

The review summary (Volume 1) and the complete technical reports (Volume 2) for all registrations and approvals relating to fipronil are available from the APVMA web site <http://www.apvma.gov.au/>.

## Submissions from the public are invited

This Preliminary Review Findings report:

- outlines the APVMA review process
- advises interested parties how to respond to the review
- summarises the technical assessments from the reviewing agencies
- outlines the proposed regulatory action to be taken in relation to the continued registration of fipronil products.

The APVMA invites persons and organisations to submit their comments and suggestions on this Preliminary Review Findings report directly to the APVMA. The comments will assist the APVMA in preparing the Review Findings report, which is the second report in the three-stage review reporting process. The final report is the Final Review Report and Regulatory Decision.

## Preparing your comments for submission

You may agree or disagree with or comment on as many elements of the preliminary review findings as you wish.

When making your comments:

- clearly identify the issue and clearly state your point of view
- give reasons for your comments, supporting them, if possible, with relevant information and indicating the source of the information you have used
- suggest to the APVMA any alternative solution you may have for the issue.

Please try to structure your comments in point form, referring each point to the relevant section in the preliminary review findings. This will help the APVMA assemble and analyse all of the comments it receives.

Finally please tell us whether the APVMA can quote your comments in part or in full.

Please note that subject to the *Freedom of Information Act 1982*, the *Privacy Act 1988* and the Agvet Codes, all submissions received may be made publicly available. They may be listed or referred to in any papers or reports prepared on this subject matter.

The APVMA reserves the right to reveal the identity of a respondent unless a request for anonymity accompanies the submission. If no request for anonymity is made, the respondent will be taken to have consented to the disclosure of their identity for the purposes of Information Privacy Principle 11 of the *Privacy Act 1988*.

The contents of any submission will not be treated as confidential or confidential commercial information unless they are marked as such and the respondent has provided justification such that the material is capable of being classified as confidential or confidential commercial information in accordance with the *Freedom of Information Act 1982* or the Agvet Codes as the case may be.

THE CLOSING DATE FOR SUBMISSIONS IS 2 August 2011

Submissions can be sent either by email to chemicalreview@apvma.gov.au or by mail to:

Manager Fipronil Review
Australian Pesticides &Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604

Telephone: 61 2 6210 4700
Facsimile: 61 2 6210 4776
Email: chemicalreview@apvma.gov.au

# EXECUTIVE SUMMARY

## Introduction

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has undertaken a comprehensive review of fipronil in line with reconsideration of the approval and registration of this active constituent in Australia. This Preliminary Review Findings report summarises the data evaluated and the proposed recommendations arising from the review of fipronil in agricultural and veterinary situations.

Fipronil is a broad-spectrum insecticide used in both agricultural and veterinary situations. It controls insect pests in a wide range of agricultural crops, it is used as an insecticidal seed dressing, and it is used for the control of termites, cockroaches and ants in residential and commercial buildings. In veterinary situations, fipronil products are used as spray or concentrated spot-on formulations to control fleas, ticks and other ectoparasites on dogs and cats, and the products are used for the treatment and control of flea allergy dermatitis.

Fipronil was nominated for review following a number of reports of adverse experiences involving the use of products containing fipronil. Reports of adverse effects were first received in 1996 and have been recorded in every reporting period since. Reports primarily involved veterinary chemical products and included skin reactions in animals and humans, neurological signs and deaths in target animals (often involving concurrent infestations with paralysis ticks), and deaths following off-label use in domesticated rabbits. Very few adverse experience reports have been received for agricultural products; however, it should be noted that the AVPMA did not have a formal adverse experience reporting program for agricultural products at the commencement of the review. The adverse experience reporting program for agricultural chemical products commenced in October 2003.

Continuing receipt of adverse experience reports at a steady rate up to 2002 raised concerns about the safety of fipronil.

These ongoing concerns in relation to human health and the safety of target and non-target animals prompted the APVMA to undertake a review of fipronil as part of the APVMA's Review Program.

At the commencement of the review there were four active constituent approvals and 29 registered products containing the active constituent fipronil for agricultural and veterinary use in Australia (refer to the product list in Appendix A).

## Preliminary review findings

### Toxicological assessment

The toxicological assessment for the review of fipronil was undertaken by the Office of Chemical Safety and Environmental Health (OCSEH). This assessment considered all the toxicological data and information submitted for the review together with all previously submitted registration data and relevant published data.

The primary route of exposure to humans and animals is by the dermal route, although exposure by inhalation and of the eyes may also occur. Fipronil was considered to be a slight eye and skin irritant. Although some adverse experience reports have reported dermal reactions in humans following fipronil exposure to veterinary products, the data do not reliably demonstrate fipronil to be a skin sensitiser. Fipronil does not present a genotoxic hazard or reproductive toxicity hazard.

Available evidence suggests that the metabolism of fipronil is qualitatively similar across laboratory mammalian species except the rabbit, whose slow metabolism may explain its increased sensitivity to fipronil in comparison to other species.

On the basis of the review of all the toxicity data it was concluded that there should be no change to the approval status of fipronil or to the ongoing registration of existing fipronil products in Australia. However, some amendments have been recommended for the first aid instructions and safety directions for products available in Australia.

Taking into consideration the information available for the review, the OCSEH was also able to make the following recommendations in relation to the health standards for fipronil:

- Affirm the Acceptable Daily Intake (ADI) of 0.0002 mg/kg bw/day (milligrams per kilogram of body weight per day), based on a No Observed Effect Level (NOEL) of 0.02 mg/kg bw/day in a chronic carcinogenicity study in rats (a group value to cover fipronil, desulfinyl fipronil and fipronil sulphide).
- Affirm the Acute Reference Dose (ARfD) of 0.02 mg/kg bw, based on a NOEL of 2.5 mg/kg bw/day for reduced landing footsplay in an acute oral neurotoxicity study in rats and the application of a 100-fold safety factor (also a group value).
- Fipronil is in S6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with a cut-off to S5 at 10%, and is unscheduled at 0.05% fipronil or less. As there has been no new information provided to this review that indicates that these levels are inappropriate, it is recommended that the current scheduling of fipronil be maintained.

## Occupational health and safety assessment

The occupational health and safety assessment for the review of fipronil was undertaken by the OCSEH, which considered all the occupational health and safety data and information submitted for the review.

Very limited specific exposure data are available for fipronil. Therefore occupational exposure to fipronil was estimated using surrogate data from the Pesticide Handlers Database (PHED USEPA 1999).

Considering the mode of action of fipronil, the endpoint most relevant for the occupational health and safety (OHS) risk assessment was based on neurotoxicity.

The most likely route of exposure to fipronil would be by dermal contact with the product and treated material i.e. vegetation or animal. Inhalation of spray aerosols may also occur. Dermal and inhalation studies were considered appropriate for selecting the NOELs for risk assessment: NOELs from short-term studies were considered to be representative of the use of fipronil.

The APVMA considered the advice received from the OCSEH and makes the following recommendations relating to the continued use of products containing fipronil:

- revision to safety directions for some fipronil products
- addition of a rehandling statement for fipronil veterinary spray products
- new or revised re-entry intervals for agricultural uses.

### Animal safety assessment

The APVMA engaged an external reviewer to assess the published and unpublished animal safety data for fipronil. This included a literature review of information available in the public domain, as well as adverse experience reports provided to the APVMA and animal safety studies provided by the registrant.

Skin reactions appear to be the most common adverse experience reported for fipronil in dogs and cats, both globally and in Australia. While the incidence of these reactions is low, there appears to be a real and characteristic reaction to fipronil-containing products in target animals.

While local skin reactions are unlikely to endanger the overall health of the animal, they may be of concern to owners. These reactions, which may include clinical signs of alopecia, acute moist dermatitis, erythema and pruritus, are unlikely to cause serious signs of disease in affected animals, but may cause distress to owners and the affected animals.

A close examination of the published and unpublished information for dogs and cats suggests that fipronil-containing products are generally safe to use in the healthy target species at recommended dose rates and routes of administration.

Additional label warnings in relation to the application of fipronil products are recommended. This includes warnings about the possibility of cutaneous reactions in dogs and cats treated with the spot-on formulations, avoiding applying fipronil products to ‘non-healthy’ skin, and for the spray, treating animals in open areas, and ensuring they are not placed in confined spaces until the spray has dried.

Fipronil is not recommended for use in non-target animals, especially rabbits, due to their increased sensitivity to fipronil and severity of reactions (including death). Additional label warnings are recommended.

Based on consideration of the available information and the recommended label changes, the continued use of fipronil-containing products when applied to dogs and cats is considered safe.

## Public submissions

In addition to specific studies provided by registrants and approval holders, submissions were received from the public in relation to the review of fipronil. These were received from industry groups, the National Toxics Network and an individual. The submissions are summarised in Section 3.5.

## Proposed review recommendations

After consideration of all data including the additional assessments, the APVMA proposes the following regulatory actions:

a) Affirm active constituent approvals (Appendix A).

To satisfy the requirements for continued registration of products, the APVMA proposes to:

b) Vary label approvals for all products in Appendix A as follows:
   - inclusion of the amended safety directions for fipronil-containing products
   - inclusion of new or amended re-entry intervals and rehandling periods
   - inclusion of appropriate warnings relating to animal safety

c) Affirm product registrations.

If the proposed label variations are made, then the product registrations and label approvals of all products (Appendix A) can be affirmed.

d) Cancel product label approvals.

The APVMA proposes that all previously approved label approvals be cancelled. The basis for this is that they do not contain adequate instructions in relation to the continued requirements for registration and approval.

# 1 INTRODUCTION

The APVMA has reviewed the approval of the active constituent fipronil, registered products containing fipronil and the associated label approvals for products containing fipronil. This document summarises the data evaluated and the proposed recommendations from the review.

## 1.1 Regulatory status of fipronil in Australia

Fipronil is a broad-spectrum insecticide first used in Australia in 1994 as an agricultural chemical product. The veterinary chemical use of fipronil has been registered since 1995.

At the commencement of the review, there were four active constituent approvals for fipronil and 29 registered products containing the active constituent fipronil. These active constituent approvals and product registrations are subject to this review. Any new active constituent approvals and product registrations that occur after the commencement of the review are subject to the outcomes of the review. Since the commencement of the review, there have also been a number of product registrations that have lapsed and active constituent approvals cancelled at the registrant or approval holder's request.

Details of all active approvals and product registrations are provided in Appendix A.

## 1.2 Reasons for fipronil review

The active constituent fipronil, all products containing fipronil and their associated labels were placed under review because of concerns over toxicological, occupational health and safety, and animal safety issues.

The APVMA's Adverse Experience Reporting Program received adverse experience reports for products containing fipronil, primarily in veterinary chemical products. Continuing receipt of such reports at a steady rate, particularly during the three years to 2002, raised concerns about the safety of fipronil, although the incidence of adverse experience reports for products containing fipronil was relatively low (reporting incidence less than 0.01%).

Reports of adverse experiences in target and non-target animals associated with the use of fipronil were first received in 1997 and have been recorded in every reporting period since then. Of the 120 animal reports received prior to the commencement of the review, 80 were classified by the APVMA as possibly or probably linked to product use on cats and dogs. A further 27 reports were linked to off-label product use in rabbits.

Clinical signs reported in animals include skin reactions and neurological signs followed in some cases by death. There were 56 suspected adverse experience reports for dogs classified as being either probably or possibly associated with fipronil. In 21 of those reports (38%) there was concurrent infestation with the dog paralysis tick, *Ixodes holocyclus*. Of these reports, nine involved death of the dog. Products containing fipronil are registered for control of paralysis tick under specific precautionary instructions, including daily checking of animals at risk of infestation, since ticks that have become attached prior to treatment are not killed by treatment. Also, ticks that may have attached immediately after treatment may not be killed by fipronil treatment. In two cases, neurological excitation without death was reported. In the remaining cases, a range of adverse effects including skin reactions was reported.

In addition to the adverse experiences in animals, some of the reports involved suspected adverse experiences in humans. The first of these reports of suspected adverse experiences in humans were received in 1996 for the veterinary spray formulation and involved reactions in humans who had applied the spray to pets. Prior to the commencement of the review, 53 reports of suspected adverse experiences in humans involving both the spray and the concentrated spot-on formulation had been received. Of these reports, 43 were considered by the APVMA as possibly or probably linked to product use. Skin reactions have been the predominant adverse experience reported for humans. Some reactions did not occur during the application of the products but after skin contact with the treated cat fur or dog hair.

Therefore ongoing concerns in relation to human health and target and non-target animal safety prompted the APVMA to undertake a review of fipronil.

## 1.3 Scope of the review

When the extent of the review was scoped, the reasons for the nomination of fipronil, the information already available on this chemical and the ways that it is approved for use in Australia were taken into account.

The basis for a reconsideration of the registration and approvals for a chemical is whether the APVMA is satisfied that the requirements prescribed by the Agvet Codes for continued registration and approval are being met. In the case of fipronil, these requirements are that the use of the product in accordance with the instructions for its use:

- would not be an undue hazard to the safety of people exposed to it during its handling; and
- would not be likely to have an effect that is harmful to human beings; and
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

The APVMA reviewed the toxicological, occupational health and safety and animal safety conditions of registration and approval for fipronil.

The APVMA took into consideration the following matters relevant to active constituent approvals, product registrations and label approvals for fipronil:

- the toxicity of fipronil, primarily in relation to dermal irritation and the induction of skin sensitisation
- the toxicity of photodegradation products of fipronil, particularly in relation to neurotoxicity and dermal toxicity
- toxicological effects associated with products containing fipronil, including the potential to form toxic photodegradation products
- occupational health and safety issues including the risk to workers mixing, loading and applying products containing fipronil or users using products containing fipronil
- risks to workers on re-entry to treated areas or humans handling animals after they have been treated
- animal safety

- adequacy of label instructions, including the suitability of personal protective equipment, specified re-entry intervals, and other warnings or precautionary instructions.

The APVMA also considered whether product labels carried adequate instructions and warning statements. Such instructions should include:

- the circumstances in which the product should be used
- how the product should be used
- times when the product should be used
- frequency of the use of the product
- the withholding period after the use of the product
- disposal of the product and its container
- safe handling of the product.

On the basis of these concerns, it was decided that the active constituent approvals, product registrations and label approvals for fipronil be reviewed under the provisions of Part 2, Division 4 of the Agvet Codes.

## 1.4 Regulatory options

There can be three possible outcomes to the reconsideration of the active constituent fipronil, registration of products containing fipronil and all associated label approvals. Based on the information reviewed the APVMA may:

- be satisfied that the products and their labels continue to meet the prescribed requirements for registration and approval and therefore affirms the registrations and approvals
- be satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration and approval will be complied with and therefore varies the conditions of registration or approval
- be not satisfied that the requirements for continued registration and approval continue to be met and thus suspends or cancels the registration and/or approval.

# 2 APPROVED FIPRONIL USE PATTERNS

## 2.1 Fipronil use patterns

### 2.1.1 Agricultural applications

In agriculture, fipronil products are used to control a wide range of insect pests in bananas, brassicas, cotton, potatoes, grapes, sugarcane and mushrooms. In broadacre crops, fipronil products are applied by ground or aerial application; hand-held application is also used in some crops such as bananas and grapes.

Fipronil is also used as an insecticidal seed dressing in rice, canola, sorghum and cotton for the control of mites, worm and thrips. It is also available in ultra low volume sprays to control locusts in pasture and sorghum. A granular formulation is registered for use in recreational domestic and commercial turf. The granules are evenly spread by mechanical spreaders and then incorporated by rainfall or irrigation. Fipronil is also used to control termites, cockroaches and ants in residential and commercial buildings.

### 2.1.2 Veterinary applications

The veterinary use of fipronil has been registered since 1995. Veterinary products containing fipronil are marketed for use on cats and dogs as ready-to-use spray or concentrated spot-on formulations. A number of the spot-on products also include the active constituent, (S)-methoprene. The products are intended for the control of fleas and other ectoparasites such as ticks, biting lice and sarcoptic mange, as well as the treatment and control of flea allergy dermatitis. The products are mostly applied by pet owners but may also be used by veterinarians and pet groomers. The spot-ons are applied monthly to dogs and cats, except for paralysis tick control in dogs, where the products are applied fortnightly. For cats, the spray is applied every three to eight weeks; and to dogs it is applied every three to 12 weeks.

Use of the spot-on range of products involves breaking the snap-off top from the pipette, then while holding the pipette tip against the skin of the neck of the animal, squeezing the pipette several times until it is emptied of its contents. Label instructions for the spray require the user to spray the entire animal against the lay of the hair, using a pump nozzle applicator, so the product penetrates down to the skin, and the coat is thoroughly wet.

## 2.2 Label restrictions

Current withholding periods and other restrictions for fipronil products specified on the product labels are presented in Table 1.

**Table 1: Current withholding periods and other restrictions for fipronil products**

| CROP/SITUATION | WITHHOLDING PERIOD AND/OR OTHER RESTRICTIONS |
|---|---|
| Brassicas | Do not harvest for 7 days after application. |
| Cotton | Do not harvest for 4 weeks after application. Do not graze or cut for stock food. |

| | |
|---|---|
| Potatoes | Not required when used as directed. Do not graze or cut for stock food any part of failed crop (including tubers). |
| Bananas | Not required when used as directed. |
| Mushrooms | Do not harvest for 14 days after application. |
| Pastures | Do not graze or cut for stock food for 14 days after application, or withhold stock from slaughter for 21 days, whichever is appropriate. |
| Sorghum | Do not harvest, graze or cut for stock food for 14 days after application. |
| Sugarcane | Do not harvest for 12 weeks after application. Do not graze or cut for stock food for 12 weeks after application. |
| Wine grapevines | Not required when used as directed. Do not feed trash or by-products resulting from treated grapevines to livestock. |
| Seed Treatment: | |
| | Harvest |
| Canola, sorghum, rice, sunflower and cotton | Withholding period not required when used as directed. |
| | Grazing |
| Canola | Do not graze plants grown from treated seed, or cut for stock food within 9 weeks of sowing. |
| Sorghum | Do not graze plants grown from treated seed, or cut for stock food within 5 weeks of sowing. |
| Sunflower | Do not graze plants grown from treated seed, or cut for stock food within 3 weeks of sowing. Do not feed treated seed to animals. |
| Rice | Not required when used as directed. |
| Termite treatment | Residents and pets should not be allowed in a room being treated. Any spills should be cleaned up before leaving the room. Ensure all heating and air conditioning ducts, air vents, plumbing pipes, sewer lines, floor drains, heating pipes and electrical lines and conduits are known and identified before commencing any application of termiticide. Do not puncture or contaminate any of these. Avoid application around edible plants. |
| Turf | Do not allow birds or animals to feed on treated turf. Do not feed turf clippings from any treated area to any birds or animals. |
| Veterinary use | Treat pets outside or in well-ventilated room away from surfaces likely to be affected by alcohol spray. Do not breathe spray when applying the spray – hold the applicator vertically 10-20 centimetres away from the coat. |

### 2.2.1 Re-entry and re-handling intervals

Re-entry and re-handling intervals provide instructions to users regarding entering treated areas or handling treated animals, including advice on appropriate clothing to be worn and the necessary clean up measures to be taken to reduce exposure.

# 3 SUMMARY OF DATA ASSESSMENTS

## 3.1 Toxicology

The toxicological assessment for the review of fipronil was undertaken by the Office of Chemical Safety and Environmental Health (OCSEH). The OCSEH considered all the toxicological data and information submitted for the review. The toxicological studies and findings are summarised below. The complete report is in Volume 2.

In Australia, fipronil is the active constituent in 48 currently registered products that are used for the control of a wide range of insect pests in a variety of crops and turf; in ant, cockroach and fruit fly baits; and in veterinary products for flea, tick and other ectoparasite control in cats and dogs.

Fipronil is included in Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), with cut-offs to Schedule 5 when in preparations containing 10% or less of fipronil, and is unscheduled in preparations containing 0.05% or less of fipronil. The current Acceptable Daily Intake (ADI) for fipronil is 0.0002 mg/kg bw/day (milligrams per kilogram of body weight per day) based on a No Observed Effect Level (NOEL) of 0.02 mg/kg bw/day in a two-year study in rats and including a safety factor of 100. The Acute Reference Dose (ARfD) is 0.02 mg/kg bw based on a combined NOEL of 2.5 mg/kg bw/day from two acute oral neurotoxicity studies in rats and including a safety factor of 100. Both the ADI and ARfD are group values (fipronil, desulfinyl fipronil and fipronil sulfide).

There is no National Health and Medical Research Council Health Value for fipronil in drinking water. Maximum residue limits (MRLs) have been set for fipronil in a range of vegetables, fruit, grain, herbs, spices, seeds, nuts, and oils, and in sugar cane, eggs, honey, milks, mushrooms, edible offal (mammalian and poultry) and meat (mammalian and poultry). The MRLs range from 0.005 to 0.2 mg/kg.

### 3.1.1 Summary of toxicity studies

#### ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

##### *Percutaneous absorption*

Regent 80 WDG (~80% fipronil), spiked with [$^{14}$C]-fipronil, was applied to the skin of male rats at 0.07, 0.67 or 3.88 mg/cm$^2$ (milligrams per square centimetre) for various periods of up to 24 hours (application volume = 100 microlitres (µL), area of application = 12.5 cm$^2$). At 24 hours post-application, the percentage of the applied dose that was systemically absorbed was very low (0.37, 0.40 and 0.07% in increasing order of dose). If the radioactivity in and on the skin is included, these amounts increase to 2.5, 4.1 and 0.6% respectively. Fipronil was poorly absorbed across rat skin *in vivo* (Cheng 1995).

Absorption rates of [$^{14}$C] radiolabelled fipronil (200 grams per litre (g/L) fipronil, formulation EXP60145A, equivalent to the Australian product Regent 200 SC), testosterone and hydrocortisone (20% weight for weight (w/w) suspension of each in EXP60145A), and these suspensions diluted with distilled water, were measured through human, rat or rabbit epidermal membranes *in vitro*. Fipronil generally permeated rat and rabbit skin at an approximately tenfold greater rate than human skin when applied at 200 g/L, 4 g/L or 0.2 mg/L, though at 0.2 mg/L permeation through rat and human epidermis was similar. The permeation rate of

fipronil through human skin was less than the permeation rate for hydrocortisone and testosterone, and on this basis, fipronil is a slow penetrant when applied in formulation EXP60145A (Walters and Brain 1990).

*In vitro* absorption studies through human and rat epidermis were conducted with ultra-low volume (ULV, 2.5 and 26 g/L), suspension concentrate (SC, 0.5 and 50 g/L), and emulsifiable concentrate (EC, 6 and 312 g/L) formulations of radiolabelled fipronil. The 26 g/L ULV product used in this study is similar to the current Australian product Regent 25 UL. In all cases, absorption was not proportional to the fipronil concentration applied, and the absorption rate was considerably higher through rat epidermis than through human epidermis (usually tenfold). Radioactivity retained in the epidermis was high relative to the amount that penetrated, generally more so for rat epidermis than human. The amount absorbed was greater for the higher concentrations, but the percentage absorbed was lower (Ward 1997a, 1997b, 1998).

### *Oral absorption, distribution and excretion*

The levels of radioactivity were analysed over time in the blood and tissues of rats after administration of single oral doses of 4 or 40 mg/kg bw/day [$^{14}$C]-fipronil. At 4 mg/kg bw, peak blood concentrations were achieved at 5–6 hours post-dosing, but absorption was slower at 40 mg/kg bw, with maximal blood concentrations occurring at approximately 36 hours. Elimination was slow at both doses, more so in females. Radioactivity was distributed widely in the tissues, with a similar distribution at either dose. Apart from the stomach and gastrointestinal tract and their contents, the highest levels of radioactivity were in the abdominal fat, followed by the adrenals, pancreas, thyroids, skin and fur, ovaries, uterus and the liver (Totis and Fisher 1994).

The tissue distribution of radioactivity was studied in the rat, mouse and rabbit by whole body autoradiography at 12 and 72 hours following a single oral dose of 5 mg/kg bw [$^{14}$C] fipronil. Radioactivity was widely distributed in the tissues, being highest in brown fat, fat and the Harderian gland. Elimination was slow, as tissue concentrations were only marginally reduced at 72 hours post-dosing (Whitby 1991).

Bile duct-cannulated male and female rats were given single doses of 4 or 40 mg/kg bw [$^{14}$C]-fipronil by gavage. The major route of excretion was the faeces. The bile was also an important excretory route, and in male rats that received 40 mg/kg bw, the amount of radioactivity excreted in the bile slightly exceeded the amount excreted directly in the faeces. Excretion via the urine was relatively low in all groups. Elimination was slow, with about 80% and 60% of the administered dose remaining in the tissues 72 hours after dosing at the low and high doses, respectively. Systemic absorption was estimated to be about 90% at the low dose and 80% at the high dose. The vast majority of the radioactivity in the bile comprised numerous metabolites of fipronil, with little present as the parent compound. The metabolite profiles of bile from both dose groups and either sex were qualitatively similar, though most components were not chemically defined (Totis 1995).

### *Distribution and metabolism*

In an unpublished paper that compared the results of metabolism studies in mice, rats, dogs, rabbits, goats, hens and fish, it was concluded that the fate of fipronil in all of these species was qualitatively similar. The quantitative differences were greatest when metabolism of fipronil in the rabbit was compared with the rat, mouse and dog (Savage 1993).

Brain and blood samples were analysed for fipronil, MB 4590 (fipronil sulfide) and MB 46136 (fipronil sulfide) from male mice fed 100 parts per million (ppm) (approximately equal to 15 mg/kg bw/day) fipronil in the diet

for 14 days, or 75 and 150 ppm over 28 days (approximately equal to 11 and 22 mg/kg bw/day), or until mortality reached 50%. Fipronil was detected in the brain of one mouse in the 100 ppm group that died prematurely, but otherwise only MB 46136 (fipronil sulfone) was detected in the blood and brain tissue of treated mice. Mice that died did not have higher levels of fipronil or MB 46136 (fipronil sulfone) in the brain than survivors (Fisher 1991, 1992).

Rats were given a single oral dose of [$^{14}$C]fipronil at 4 or 150 mg/kg bw, or repeat doses of 4 mg/kg bw/day (unlabelled) for 14 days, followed by a radiolabelled dose on day 15. The major route of excretion was the faeces, from which up to 45% of the radiolabel was recovered at the single low dose, 75% at the high dose, and 60% after repeated dosing for the period up to 168 hours post-treatment. Relatively low levels were found in the urine (up to 6, 16 and 29% after single low, single high and repeat dosing, respectively). Much of the radioactivity was recovered from the tissues (up to 45% at the single low dose, with the highest concentration detected in the fat) and about 20% after repeated dosing, but only 3–5% at the high dose. Fipronil was metabolised rapidly, with numerous metabolites found in both the faeces and urine. The major metabolite detected in the tissues was MB 46136 (fipronil sulfone), with unchanged fipronil found only in the faeces. After the single low dose, blood radioactivity peaked at 4–6 hours, but elimination was slow (blood half-life up to 200 hours after the single low dose), indicating a potential for bioaccumulation. Peak blood concentration was approximately in proportion to dose, but at 150 mg/kg bw, the absorption phase was longer, and the elimination phase shorter than at the low dose of 4 mg/kg bw (Powles 1992).

Bile was collected from a group of rats given single oral doses of 4 mg/kg bw [$^{14}$C]-fipronil for 72 hours post-dosing. The collected bile was then infused over a 24-hour period into the duodenum of a second group of rats. For both groups, at least 70% of the radioactivity was absorbed. In the orally dosed group, 13% of administered radioactivity was recovered in the bile, 16% in the faeces, and less than 3% in the urine, with 59% in the tissues. The latter comprised 34% in the residual carcass, with the liver, skin and gastrointestinal tract contents accounting for most of the remainder. In comparison to the orally dosed group, the infused group had a similar amount of administered radioactivity in the faeces, slightly more in the urine, considerably more in the bile (38%), but only about 26% in the tissues. This study demonstrated that fipronil metabolites excreted in the bile may be reabsorbed and redistributed into the tissues (Kemp 1999).

Preliminary to a comparative metabolism study, mice (Broadmeadow 1991a), rats (Broadmeadow 1991b) and rabbits (Cummins 1991) were treated with 0.4 or 4 mg/kg bw/day [$^{14}$C]-fipronil for up to 14 days, followed by a reversibility period of up to 7 days. There were no deaths, no clinical signs of toxicity, or effects on bodyweight gain or food consumption. In the main study, in all species the principal metabolite in the tissues was MB 46136 (fipronil sulfone). At 0.4 mg/kg bw/day, MB 46136 (fipronil sulfone) increased over the dosing period, with levels greatest in fat, followed by thyroid, liver, brain and blood. At 4 mg/kg bw/day, maximum levels of radioactivity were achieved earlier in rats and mice than in rabbits, the latter also showing relatively long elimination times. The parent compound was detected in tissues, particularly during the first 24 hours of dosing, and remained longest in the fat, particularly in rabbits. Fipronil sulfone (MB 46136) was found in the tissues in trace amounts, with RPA 200766 (fipronil amide) below the limit of quantification (Brockelsby 1991).

In a comparative metabolism study in rabbits, rats and mice, elimination of radiolabel was slow following single oral doses of 5 mg/kg bw [$^{14}$C]-fipronil. A large percentage of the dose had not been excreted at 7 days post-dosing (80% in rabbits, 40% in rats, and 60% in mice). Calculated elimination half-lives were approximately 14 days for rabbits, and 3 days for rats and mice. The highest concentrations of

fipronil/metabolites were in the fat (rabbit > rat > mouse). For liver, kidney, muscle, brain and thyroid, little difference in radioactivity levels was seen between rat and mouse, but radioactivity was generally higher in rabbits. No significant levels of radiolabelled carbon dioxide were found in trapped air. The principal tissue metabolite was MB 46136 (fipronil sulfone), with traces of fipronil and MB 45950 (fipronil sulfide). Fipronil, fipronil sulfide and fipronil sulfone were found in the faeces (Lowden and Savage 1991).

Radiolabelled fipronil was incubated with rat or rabbit hepatocytes for 0, 1, 3, 5 or 24 hours to compare the metabolic pathways. Thin layer chromatography showed that fipronil was metabolised completely by rat hepatocytes, and partially by rabbit hepatocytes. High performance liquid chromatography analysis showed that both rat and rabbit hepatocytes metabolised fipronil to MB 46136 (fipronil sulfone, the principal metabolite). RPA104615 (fipronil detrifluoromethyl sulfonate) was also detected in the 24-hour incubation samples for both species, but this was considered likely to represent a product of the photolytic degradation of fipronil sulfone. Results indicated that rat hepatocytes metabolised fipronil faster than rabbit hepatocytes (Guyomard 1993; Fisher 1992).

When fipronil was incubated with rat or human liver microsomes, fipronil sulfone was the only metabolite detected. The $K_m$ values for fipronil metabolism were similar in rat and human microsomes, but the $V_{max}$ in the rat was approximately three times that in humans. There was a 40-fold variation in the rate of fipronil metabolism across human microsomes from 19 individuals, which correlated with levels of CYP3A4 and CYP2C19 (Tang et al. 2004).

## ACUTE TOXICITY STUDIES

### *Active constituent*

When administered by the oral route, fipronil was moderately toxic to mice ($LD_{50}$ = approximately 91 mg/kg bw) (Mondot and Dange 1995) and rats ($LD_{50}$ = 97 mg/kg bw) (Gardner 1988a). Dermal toxicity was low in rats ($LD_{50}$ >2000 mg/kg bw; aqueous suspension) and moderate in rabbits ($LD_{50}$ = 354 mg/kg bw; corn oil) (Gardner 1988b, Myers and Christopher 1992). Inhalation toxicity was moderate in rats ($LC_{50}$ = 682 mg/m$^3$; or 360/420 mg/m$^3$ in males/females) (Cracknell 1991; Nachreiner 1995). Toxicological signs were consistent with the known mode of action for fipronil as a gamma-aminobutyric acid (GABA) antagonist, and included hyperactivity, abnormalities of gait and posture, tremors and convulsions. Necropsy findings were limited to dermally exposed rabbits in which there were effects on the lungs, kidneys and spleen (e.g. discolouration, enlargement, blood in urine, kidneys).

Fipronil moistened with water was not a skin irritant in rabbits (Liggett 1988a), but it was a slight skin irritant in another study that had used corn oil as the vehicle (Myers and Christopher 1993a). Two eye irritancy studies in rabbits reported low levels of irritation, but differed in the time for which symptoms persisted. Overall, fipronil was a slight eye irritant (Liggett 1988b, Myers and Christopher 1993b). Fipronil was not a skin sensitiser in guinea pigs, with no evidence of a skin sensitisation potential seen in a Buehler assay (Smith 1990) and maximisation test of Magnusson and Kligman (Johnson 1993).

In rats, MB 46513 (desulfinyl fipronil) showed high acute oral toxicity (median lethal dose ($LD_{50}$) = 18/15 mg/kg bw, males/females; Dange 1993a) and low acute dermal toxicity ($LD_{50}$ >2000 mg/kg bw; Dange 1993b). In the oral study, deaths occurred on days two to four, preceded by convulsions. Clinical signs in

both studies were consistent with neurotoxic effects. The livers of decedents were enlarged, with various pathological changes including pale colour, foci of necrosis, and early fibrosis.

The acute oral toxicity of MB 45950 (fipronil sulfide) in rats was moderate when administered in corn oil ($LD_{50}$ = 83 mg/kg bw; Dange 1994a), but in another study that used water as the vehicle, it had low acute oral toxicity ($LD_{50}$ = 580 mg/kg bw; Haynes 1988a). Toxicity was characterised by piloerection, red staining of the fur, hypoactivity and convulsions. In both studies, males were more susceptible than females. When applied undiluted to rat skin, the dermal $LD_{50}$ was >500 mg/kg bw (Haynes 1988b). In rabbits, MB 45950 (fipronil sulfide) was a slight eye irritant, but was not a skin irritant (Haynes 1987a,b).

Fipronil sulfone (MB 46136) had moderate acute oral toxicity when administered to rats in corn oil ($LD_{50}$ = 218 mg/kg bw; Gardner 1988c). Clinical signs included abnormal gait, lethargy, pallor of the extremities, diarrhoea, increased respiratory rate, ataxia, increased salivation and convulsions. In aqueous suspension, the dermal $LD_{50}$ in rats was >2000 mg/kg bw (Gardner 1988d). When applied undiluted to rabbits, MB 46136 (fipronil sulfone) was not a skin irritant, but it was a slight eye irritant (Liggett 1988c,d).

The acute oral toxicity of RPA 105048 (fipronil desulfinyl amide) was moderate in rats ($LD_{50}$ = 467 mg/kg bw), with clinical signs of neurotoxicity similar to MB 46513 (desulfinyl fipronil) (Dange 1994f). The other metabolites of fipronil that were tested [RPA 200766 (fipronil amide), RPA 200761 (fipronil carboxylic acid), RPA 105320 (fipronil sulfonyl amide), and RPA 104615 (fipronil detrifluoromethyl sulfonate)] all had low acute oral toxicity in rats. The $LD_{50}$ values for these compounds were greater than 2000 mg/kg bw, with no deaths (Katchadourian 1995; Dange 1994e, 1993c,d).

### *Products and formulations (Australian)*

The acute oral toxicity of Regent 200 SC Insecticide (suspension concentrate, 200 g/L) in aqueous vehicle was low in rats ($LD_{50}$ = 1099 mg/kg bw) and moderate in mice ($LD_{50}$ = 324 mg/kg bw) (Dreher 1990a,b). The dermal toxicity was low ($LD_{50}$ > 4192 mg/kg bw and $LD_{50}$ = 2493 mg/kg bw in rats and rabbits respectively) (Dreher 1990c,d). Inhalation toxicity in rats was moderate ($LC_{50}$ = 1070 mg/m$^3$) (Blagden 1993a). The product was a slight skin irritant and a moderate eye irritant in rabbits, and did not cause skin sensitisation in guinea pigs in a modified Buehler assay (Dreher 1993a; Glaza 1997; Dreher 1993b).

Acute studies were conducted with a 1 g/kg GR product (Code EXP60819A), similar to the product marketed in Australia, Chipco Choice Insecticide (1 g/kg GR), but differing in the carrier. This product had low acute oral ($LD_{50}$ > 5000 mg/kg bw), dermal ($LD_{50}$ > 2000 mg/kg bw), and inhalation ($LC_{50}$ > 5160 mg/m$^3$) toxicity in rats (Myers 1994a,b; Nachreiner 1994). No deaths were seen in any of these studies. The product was a slight eye irritant, but not a skin irritant in rabbits, and was not a skin sensitiser in guinea pigs in a Buehler assay (Myers 1994c,d; Myers and Nachreiner 1994).

Regent 500 FS Seed Dressing Insecticide (500 g/L SC, EXP80415, equivalent to Cosmos Insecticidal Seed Treatment) had moderate oral toxicity ($LD_{50}$ = 290 mg/kg bw), low dermal toxicity ($LD_{50}$ > 2000 mg/kg bw) and moderate inhalation toxicity ($LC_{50}$ = 260 mg/m$^3$) in rats (Allen 1993a,b; Blagden 1993b). It was a slight skin irritant, but it was not an eye irritant in rabbits, and it was not a skin sensitiser in guinea pigs using the modified Buehler assay (Allen 1993c,d,e).

Frontline Spray (suspension concentrate, 2.5 g/L) had low acute oral toxicity ($LD_{50}$ > 5000 mg/kg bw) and low dermal toxicity ($LD_{50}$ > 2000 mg/kg bw) in rats (Clouzeau 1993a,b). Inhalation toxicity in the rat was also

low ($LC_{50}$ > 5060 mg/$m^3$) (Robinson 1993). The formulation caused moderate eye irritation, but no skin irritation in rabbits (Clouzeau 1993d,c). It was not a skin sensitiser in guinea pigs in a Buehler assay (Clouzeau 1993e).

Frontline Spot On for Cats and Frontline Spot On for Dogs containing 100g/L of fipronil, had low oral ($LD_{50}$ = 3000 mg/kg bw), dermal ($LD_{50}$ > 5000 mg/kg bw) and inhalation ($LC_{50}$ > 6320 mg/$m^3$) toxicity in rats (De Jouffrey 1994a,1995; Kieran 1995). The formulation was a slight skin irritant and a moderate eye irritant in rabbits (De Jouffrey 1994bc). It was not a skin sensitiser in guinea pigs using the Buehler assay (De Jouffrey 1994d).

Frontline Plus for Cats was a slight skin irritant and a slight eye irritant in rabbits (Findlay 1999a,b). It was not a skin sensitiser in guinea pigs using the modified Buehler assay (Findlay 1999c).

Regent 25 ULV Insecticide, a product of similar formulation and toxicity profile to current Australian registered fipronil UL products, had low acute oral toxicity (3208 mg/kg bw), low acute dermal toxicity (> 4000 mg/kg bw) and low acute inhalation toxicity ($LC_{50}$ > 5000 mg/$m^3$) in rats (Warshawsky 1995a,b; Hilaski 1995). It was a slight eye irritant but not a skin irritant in rabbits, and it was not a skin sensitiser in guinea pigs using the Buehler assay (Warshawsky 1995c,d,e).

Goliath Cockroach Bait (0.5% fipronil) had low acute oral toxicity in rats ($LD_{50}$ > 2000 mg/kg bw) and low dermal toxicity in rabbits ($LD_{50}$ > 2000 mg/kg bw) (Mercier 1996a1995). It was a slight eye irritant, but not a skin irritant in rabbits, and was non-sensitising to the skin of guinea pigs using the modified Buehler assay (Mercier 1996b,c,d).

Goliath Gel Cockroach Bait had low acute oral toxicity in male rats ($LD_{50}$ = 4400 mg/kg bw) and low acute dermal toxicity in rats ($LD_{50}$> 5000 mg/kg bw). The formulation was not a skin or an eye irritant in rabbits, and was non-sensitising to the skin of guinea pigs using the maximisation test of Magnusson and Kligman (Grunert 1996a–e).

Regent 800 WDG Insecticide (containing 800 g/kg fipronil) had moderate acute oral toxicity ($LD_{50}$ = 177 mg/kg bw) and moderate acute inhalation toxicity ($LC_{50}$ = 630 mg/$m^3$) in rats, and moderate dermal toxicity ($LD_{50}$ = 569 mg/kg bw) in rabbits (Allen 1994a, Blagden 1994, Allen 1994b). It was a moderate eye irritant and a slight skin irritant in rabbits, and did not cause skin sensitisation in guinea pigs using the maximisation test of Magnusson and Kligman (Allen 1994c,d,e).

## SHORT-TERM REPEAT-DOSE TOXICITY STUDIES

In a six-week study in mice, fipronil was administered in the diet at 0, 15, 40, 300 or 800 ppm, equal to (male/female) 0/0, 2.4/2.9, 6.5/8.2, 20/22 and 37/43 mg/kg bw/day respectively. All mice at 300 and 800 ppm, and 11 males and four females at 110 ppm, died or were killed in extremis during the first 2 weeks, and two males at 40 ppm died during week 5. Clinical signs present at ≥300 ppm comprised thin build, hunched appearance, piloerection, respiratory abnormalities, pallor, body tremors and abnormal gait and posture. Some mice at ≥300 ppm had convulsions, with irritability and/or overactivity observed at ≥40 ppm from weeks 2 or 3. Food consumption was decreased in males at ≥15 ppm and females at ≥110 ppm, with associated bodyweight loss or reduced bodyweight gain. Liver weights were increased in a dose-related manner in all treated groups, with histopathological findings in the liver (mainly fatty vacuolation) increased in incidence and severity at all doses relative to controls. A NOEL was not achieved in this study due to

increased liver weights and accompanying histopathology in both sexes, and reduced bodyweight gain in males at all doses. The LOEL was 2.4 mg/kg bw/day (Holmes 1990).

In a four-week dietary study, fipronil was administered to rats at 0, 25, 50, 100, 200 or 400 ppm, equal to 0/0, 3.4/3.5, 6.9/6.7, 12.6/12.9, 24.5/24.9 and 45.3/54.9 mg/kg bw/day respectively. One 400 ppm female died during week 1. Bodyweight loss or reduced bodyweight gain occurred at ≥100 ppm and was related to decreased food consumption. Platelet numbers were increased in males at ≥200 ppm. Liver weights were increased in all groups, accompanied by minimal hepatocyte enlargement at ≥100 ppm. Thyroid weights were increased, particularly in females, and minimal thyroid follicular hypertrophy was noted in all treated groups. A NOEL was not established due to increased liver weights and thyroid follicular hypertrophy at all dose levels tested (Peters et al. 1990).

Dogs were dosed orally with capsules containing fipronil at 1 or 20 mg/kg bw/day for 4 weeks, or 0 or 10 mg/kg bw/day for 6 weeks. No animals died, but clinical signs were observed at 20 mg/kg bw/day, including underactivity, hunched posture, thin appearance, head nodding, facial twitching, continuous swallowing and abnormal posture or jerking of forelimbs, with a possible convulsive episode in one female on day 9. Head nodding was also reported for one female at 10 mg/kg bw/day. Reduced food consumption and associated weight loss occurred in dogs at 20 mg/kg bw/day. At the 3-week neurological examination, exaggerated flexor reflexes, head jerks or head nodding were noted in animals at ≥10 mg/kg bw/day, with increased levels of haemoglobin and red blood cell counts in some animals in these groups, and slightly elevated albumin and total protein at 20 mg/kg bw/day. The NOEL was 1 mg/kg bw/day based on neurological signs and increased haemoglobin and red blood cell counts at ≥10 mg/kg bw/day (Holmes 1991a).

Rabbits were exposed dermally to fipronil over a 21-day period (5 days/week) at 0, 1, 5 or 10 mg/kg bw/day, under occluded dressings. Near the end of the study, two rabbits at 10 mg/kg bw/day had an episode of extreme hyperactivity. Also at 10 mg/kg bw/day, rabbits exhibited decreased food intake and decreased bodyweight gain. There were no observable effects at 5 mg/kg bw/day (Hermansky and Wagner 1993).

## SUBCHRONIC TOXICITY STUDIES

Rats were fed fipronil in the diet for 13 weeks at concentrations of 0, 1, 5, 30 or 300 ppm, respectively equivalent to 0/0, 0.07/0.07, 0.33/0.37, 1.93/2.28 and 19.9/24.0 mg/kg bw/day in males/females. No deaths or clinical signs were observed, but food intake and bodyweight gains were initially depressed at 300 ppm. Total plasma proteins (globulins) were increased at 300 ppm. At ≥30 ppm, liver and thyroid weights were increased in both sexes, with an associated increased incidence of follicular cell hypertrophy and hyperplasia of the thyroid in both sexes at the top dose, and in 30 ppm males. The NOEL was 0.3 mg/kg bw/day, due to increased liver and thyroid weights at 2 mg/kg bw/day (Holmes 1991b).

Fipronil was administered to dogs in capsules at 0, 0.5, 2 or 10 mg/kg bw/day for 13 weeks. Dogs treated at 10 mg/kg bw/day showed convulsions, tremors, head nodding, hunched posture, underactivity, inappetence, emaciation, disorientation, ataxia, apparent blindness, irregular heart rate, limb jerks and constricted pupils. Four dogs in this group were sacrificed in extremis in week 2. In dogs receiving 2 mg/kg bw/day or less, there were no deaths, and apart from inappetence, no treatment related signs. Bodyweight loss, or decreased bodyweight gain occurred at ≥2 mg/kg bw/day. Alkaline phosphatase was increased and cholesterol levels decreased in males at 10 mg/kg bw/day. The NOEL was 0.5 mg/kg bw/day due to clinical signs (inappetence) and decreased bodyweight gain at 2 mg/kg bw/day (Holmes 1991c).

## CHRONIC TOXICITY AND CARCINOGENICITY STUDIES

Groups of mice were fed fipronil in the diet at levels of 0, 0.1, 0.5, 10 or 30 ppm, equal to 0/0, 0.01/0.01, 0.05/0.06, 1.2/1.2, 3.4/3.6 mg/kg bw/day (males/females) for 53 (toxicity phase) or 78 weeks (oncogenicity phase). There were no clinical signs attributable to treatment. Mortality was not related to treatment, but unscheduled deaths were high (40–52 out of 104 individuals in the oncogenicity phase). An additional group of 72 males and 72 females that had been fed 60 ppm fipronil had low weight gains and a high death rate (14 males, 7 females) by week 9, preceded by convulsions in three cases. Weight gains at ≥10 ppm were generally decreased. Necropsies were unremarkable. Both sexes treated with 30 ppm and males receiving 10 ppm had higher liver weights than controls and an increased incidence of hepatocellular hyperplasia and chronic degenerative changes in the liver. Male mice (oncogenicity phase) at 30 ppm showed a slightly higher (but not statistically significant) incidence of malignant hepatocellular tumours. The incidence was well within the historical control range. The study provided no evidence that the administration of fipronil in the diet at levels of up to 30 ppm was carcinogenic in mice. The NOEL was 0.5 ppm, equal to 0.05 mg/kg bw/day, based on increased liver weights and microscopic changes to the liver at 1.2 mg/kg bw/day (Broadmeadow 1993).

Fipronil was fed to rats at dietary levels of 0, 0.5, 1.5, 30 or 300 ppm, equal to (males/females) 0/0, 0.02/0.03, 0.06/0.08, 1.3/1.6, 13/17 mg/kg bw/day respectively. After 52 weeks, some rats were killed, some received normal diets for a 13-week reversibility period, and others were maintained on treated diets for 89–91 weeks. The two-year study duration was shortened because of poor survival. Several rats in groups treated at ≥1.5 ppm showed neurological signs, including convulsions. These signs disappeared following cessation of treatment. Mortality was not related to treatment, except in the high dose group during the early part of the study. Bodyweight gains of the 300 ppm group were reduced during treatment. Prothrombin time was slightly decreased in females at ≥30 ppm and in 300 ppm males. Also at 300 ppm, cholesterol, calcium, total protein and globulins were increased, and albumin was decreased. Circulating thyroxine (T4) levels were consistently lower than control values in all treated groups, and this was reversible. Thyroid stimulating hormone (TSH) levels were sometimes higher at ≥30 ppm, and at least partially reversible during the recovery period. The incidence and severity of progressive senile nephropathy was increased in rats treated at ≥30 ppm. Liver and thyroid weights were significantly increased at ≥30 ppm at 52 weeks, with thyroid weights returning to normal after the recovery period. After 89–91 weeks of treatment, thyroid weights were increased in males at ≥1.5 ppm and females at ≥30 ppm. In rats treated for one year and assigned to the reversibility period, six (4/15 from the 300 ppm group) had follicular cell tumours. In the oncogenicity phase there was a significant increase in benign follicular cell adenomas for females receiving 300 ppm and for males at ≥1.5 ppm. Follicular cell carcinomas were also increased in male and female rats receiving 300 ppm compared with controls. These tumours are not considered relevant to humans. The NOEL was 0.5 ppm, equal to 0.02 mg/kg bw/day, based on clinical signs of neurotoxicity, increased thyroid weight, decreased T4 levels, and increased severity of progressive senile nephropathy at 1.3 mg/kg bw/day (Aughton 1993).

Dogs were orally dosed with fipronil in capsules at 0, 0.2, 2 or 5 mg/kg bw/day for 52 weeks. One dog receiving 2 mg/kg bw/day and two receiving 5 mg/kg bw/day were killed (in weeks 11, 31 or 34) after exhibiting convulsions, tremors, stiff limbs, gait abnormalities, lack of coordination, nervous behaviour, inappetence and bodyweight loss. All dogs receiving 5 mg/kg bw/day, and eight out of the 12 dogs receiving 2 mg/kg bw/day, showed intermittent signs of neurological disturbance (tenseness, nervous behaviour, hyperaesthesia, stiffness, abnormal gait and twitching of the facial muscles). There were no clear effects of

treatment at 0.2 mg/kg bw/day. Food consumption and growth of treated survivors were similar to that of controls, as were haematology, blood chemistry and urinalysis findings. There were no ophthalmoscopic abnormalities, and organ weights were not affected. Pathology was unremarkable. The NOEL was 0.2 mg/kg bw/day based on neurological signs and bodyweight loss at 2 mg/kg bw/day (Holmes 1992).

Dogs were dosed with fipronil at 0, 0.075, 0.3, 1 or 3/2 mg/kg bw/day via the diet for 52 weeks, the top dose being reduced from 3 to 2 mg/kg bw/day after 32 days due to compound-related toxicity. One female at 3 mg/kg bw/day was killed on day 32, having displayed signs of neurological disturbance from day 10, including convulsive episodes. Elevated haemoglobin, haematocrit, red blood cell counts, plasma alkaline phosphatase (ALP), total protein and cholesterol were observed in this dog, and liver weight was slightly increased. Neurotoxic signs were also observed in another three males and one female at 3/2 mg/kg bw/day, commencing in week 1, and in two females at 1 mg/kg bw/day in weeks in weeks 13 or 20. Some dogs at 1 and 3/2 mg/kg bw/day had periods of inappetence, but bodyweight gains were not significantly affected. Plasma analyses revealed dose-related concentrations of the parent compound and the metabolite MB 46136 (fipronil sulfone), and these did not change markedly over the treatment period. Fipronil and MB 46136 (fipronil sulfone) levels were essentially similar in both sexes, with the metabolite levels exceeding the corresponding levels for fipronil. Spleen weights were increased (24–26%) in males at 3/2 mg/kg bw/day, with a higher incidence of swollen or large spleens, and hyperplasia of the splenic red pulp. The NOEL was 0.3 mg/kg bw/day based on clinical signs of neurotoxicity at 1 mg/kg bw/day (Holmes 1993).

## REPRODUCTION TOXICITY STUDIES

Fipronil was fed to rats for two generations at dietary levels of 0, 3, 30 or 300 ppm, respectively equal to (males/females) 0/0, 0.25/0.27, 2.5/2.7 and 26/28 mg/kg bw/day. Mortality (spontaneous or humane sacrifice) was increased at ≥30 ppm in both parental generations, with deaths preceded by convulsions or other signs of neurotoxicity. At 300 ppm, reduced bodyweight gain was observed in both parental generations, and this was associated with decreased food consumption in F0 animals. At ≥30 ppm, thyroid and liver weights were increased in F0 and F1 adults, ovarian weights were decreased in the F0, and pituitary weights were reduced in the F1. In both generations, follicular epithelial hypertrophy of the thyroid was seen in males at 30 ppm, and in both sexes at 300 ppm. At 300 ppm in the F0 generation, there were reductions in mean litter size at day 1 *post-partum*, and in pup viability up to day 4. Convulsions were observed in 13 offspring from nine litters. In the F1, mating performance was slightly reduced, with a consequent reduction in fertility index. The bodyweight of 300 ppm F1 offspring at day 1 and subsequent weight gain to weaning were reduced, and tooth eruption was delayed. Also at 300 ppm, the F2 offspring had a reduced post implantation survival index, a reduced viability index at day 4 *post-partum*; mean bodyweight at day 1 *post-partum* and weight gain to weaning were lower; there was a slight delay in unfolding of the pinna, and convulsions were seen in four offspring from three litters. The parental NOEL was 3 ppm (equal to 0.25 mg/kg bw/day) due to increased thyroid and liver weights, decreased pituitary weight, and an increased incidence of follicular epithelial hypertrophy of the thyroid at 2.5 mg/kg bw/day. The NOEL for effects on the offspring was 30 ppm (equal to 2.5 mg/kg bw/day) due to clinical signs of neurotoxicity, reduced pup viability and bodyweight gain, and developmental delays at 27 mg/kg bw/day. The reproductive NOEL was 2.5 mg/kg bw/day, based on reduced litter size and pup viability in the F0 and a reduction in mating performance and fertility index in the F1 at 27 mg/kg bw/day (King 1992).

## DEVELOPMENTAL TOXICITY STUDIES

Pregnant rats were orally dosed with 0, 1, 4 or 20 mg/kg bw/day fipronil on gestation days 6–15. Maternal toxicity (decreased food consumption and bodyweight gain) was observed in 20 mg/kg bw/day dams only. There were no treatment related effects on litter values or the incidence of abnormal offspring. The NOEL for maternotoxicity was 4 mg/kg bw/day, due to decreased bodyweight gain at 20 mg/kg bw/day. The developmental NOEL was 20 mg/kg bw/day, the highest dose tested (Brooker and John 1991).

Fipronil was orally administered to pregnant rabbits on gestation days 6–19 at 0, 0.1, 0.2, 0.5 or 1 mg/kg bw/day. There was a dose-related decrease in bodyweight gain in dams at ≥0.5 mg/kg bw/day. Embryo and foetal survival, growth, and morphological development in utero were unaffected by treatment. The maternal NOEL was 0.2 mg/kg bw/day due to reduced bodyweight gain at 0.5 mg/kg bw/day. The developmental NOEL was 1 mg/kg bw/day, the highest dose tested (King 1990).

## GENOTOXICITY STUDIES

Fipronil produced negative results in *in-vitro* assays for chromosome aberration in human lymphocytes, in reverse mutation tests in bacteria, and in a gene mutation test in Chinese hamster ovary cells (Marshall 1988a; Clare et al. 1988a; Lloyd 1990). Fipronil was also negative *in vivo* in a mouse micronucleus test (bone marrow) (Edwards 1991,1995). The only positive finding was in a chromosome aberration study in Chinese hamster lung cells *in vitro* after an incubation period of 6 hours (with and without an exogenous source of metabolic activation). As clastogenicity was not observed after longer incubations (24–48 hours), this was not considered a toxicologically significant effect (Wright 1995). On the weight of evidence, fipronil was not considered to be genotoxic.

*In vitro* genotoxicity studies were also conducted on various metabolites of fipronil. The metabolites MB 46513 (desulfinyl fipronil), MB 45950 (fipronil sulfide) and MB 46136 (fipronil sulfone) were not genotoxic in reverse mutation tests in *Salmonella typhimurium* or in chromosomal aberration studies in human lymphocytes (Adams 1996a,b; Asquith 1987; Clare 1988b; Marshall 1988b,1989; Percy 1993b,1994a). Various other metabolites (RPA 200766 (fipronil carboxylic acid), RPA 104615, RPA 105320, RPA 105048, RPA 097920, RPA 200766 (fipronil sulfone amide)) were also not genotoxic in *in-vitro* tests (Percy 1993a,b,c,d,1995,1996; Allais 2002a,b). The metabolite RPA 097920 produced positive results in a chromosome aberration study using human lymphocytes, but this occurred at concentrations that caused marked cytotoxicity (Johnson 1995). Genotoxicity studies of fipronil metabolites, MB 46513 (fipronil desulfinyl) and RPA 200766 (fipronil carboxylic acid) produced negative results in rat micronucleus studies (bone marrow) *in vivo* (Proud 1996; Mehmood 2002).

## NEUROTOXICITY STUDIES

Rats were dosed once by oral gavage with fipronil in corn oil at doses of 0, 0.5, 5 or 50 mg/kg bw, and killed 16–19 days later. Six deaths (five males, one female) occurred in the high dose group, and survivors showed a variety of changes in nervous system function, including convulsions, tremors, head bobbing and myoclonic movements. At 7–8 hours post-treatment, decreases in open field activity, various reflexes, muscle tone and/or body temperature and motor activity were seen at 50 mg/kg bw, and decreased hind leg splay was observed at ≥5 mg/kg bw. The NOEL was 0.5 mg/kg bw, based on decreased hind leg splay at 5 mg/kg bw (Gill et al. 1993).

Rats were given single gavage doses of 0, 2.5, 7.5 or 25 mg/kg bw fipronil as a suspension in corn oil. At 25 mg/kg bw, staining/soiling of the head and anogenital regions was observed on day 2. During week 1, reduced bodyweight gains associated with decreased food consumption occurred in both sexes at 25 mg/kg bw, and in females at 7.5 mg/kg bw. Unusual behaviour/posture, increased grip strength, stationary position following positioning for tail pinch, reduced body temperature and decreased locomotor activity were noted at 25 mg/kg bw. At ≥7.5 mg/kg bw, landing footsplay and/or the frequency of grooming was decreased, and/or the incidence of vocalisation was increased. The NOEL was 2.5 mg/kg bw, based on reduced bodyweight gain and decreased landing footsplay at 7.5 mg/kg bw (Hughes 1997).

Fipronil was administered to rats in the diet at 0, 0.5, 5 or 150 ppm for 13 weeks (equal to 0/0, 0.02/0.03, 0.3/0.3, and 7.2/8.6 mg/kg bw/day for males/females). Early in the treatment period, food consumption and bodyweight gain were reduced at 150 ppm. No effects on nervous system structure or function were observed at any dose. In week 4 there was an increased incidence of exaggerated startle and tail pinch response in 150 ppm males, and in week 13 forelimb strength was increased in 150 ppm females. The NOEL was 5 ppm (equal to 0.3 mg/kg bw/day) due to neurobehavioural abnormalities at 150 ppm (Driscoll and Hurley 1993).

Fipronil (20 mg/kg bw/day) was administered by capsule to dogs for 5, 7 or 13 days (until signs of neurotoxicity were apparent). All dogs were then observed for at least 28 days. Signs of neurotoxicity, which were evident in all treated dogs and continued for 2–10 days post treatment, included abnormal gait, tremors, stiffening of limbs or body, convulsions, head nodding and facial twitches. One dog appeared to lose vision. Other signs included underactivity, inappetence, bodyweight loss, abnormal gait, behavioural abnormalities, hunched posture and peripheral vasodilatation. Neurological examination revealed a range of abnormalities and there was evidence of slow recovery during the reversibility period. Pathology was unremarkable (Holmes 1991d).

In a developmental neurotoxicity study, pregnant female rats were treated with fipronil in the diet at 0, 0.5, 10 or 200 ppm, from gestation day 6 to lactation day 10 inclusive. The doses were respectively equal to 0, 0.05, 0.9, and 8.7 mg/kg bw/day. Two 200-ppm dams died during the treatment period. Bodyweight loss associated with reduced food consumption was observed in 200-ppm dams on gestation days 6–10. Pup live birth index, viability index and weaning index were reduced at this dose, with reduced pup weight at ≥10 ppm throughout lactation. Delayed lower incisor eruption was noted at 200 ppm, and delays in sexual development were apparent in both sexes at 200 ppm. At 200 ppm, auditory response time was decreased, and swimming development was delayed. The maternal NOEL was 10 ppm, equal to 0.9 mg/kg bw/day, due to bodyweight loss at 8.7 mg/kg bw/day. The NOEL for pup toxicity was 0.5 ppm, equal to 0.05 mg/kg bw/day, due to reduced pup weight during lactation at 0.9 mg/kg bw/day (Mandella 1995).

### *Neurochemical effects*

In a published study that examined the effects of fipronil on the levels of serotonin and its metabolite 5-hydroxy-3-indole acetic acid in the brains of rats dosed orally with 5 or 10 mg/kg bw/day fipronil for 6 days, levels of serotonin and its metabolite in the hypothalamus, hippocampus and striatum were decreased by 26-45% relative to controls (Anadon et al. 2004)

## METABOLITE STUDIES

Studies have been conducted on a range of fipronil metabolites. The summaries of the acute and genotoxicity studies for these metabolites are presented with the corresponding studies for the active. Other studies for metabolites are summarised below.

### *MB 46513 (desulfinyl fipronil)*

Metabolism and toxicokinetics

Single doses of [$^{14}$C]-MB 46513 (desulfinyl fipronil) were administered to rats by gavage at 1 mg/kg bw or 10 mg/kg bw. A repeat oral dose experiment was also conducted at 1 mg/kg bw/day over 15 days, with radiolabelled material administered on the final day only. The rats were sacrificed 7 days after treatment. The major route of excretion was the faeces, accounting for approximately 45–70% of the radioactivity administered. Unchanged desulfinyl fipronil accounted for up to 44% of radioactivity in the faeces, along with numerous other metabolites, the latter suggestive of a role for biliary excretion, though this was not studied directly. Urine accounted for up to 11% of the administered radioactivity, comprising up to 17 metabolites, but only a trace of the parent compound. The tissues accounted for 20–41% of the administered radioactivity, which was higher in females than males. Radioactive residues were highest in the fat and the residual carcass, with unchanged desulfinyl fipronil the only radioactive compound found in tissue extracts. The high levels remaining in the tissues were consistent with the long elimination half-life in whole blood of approximately 150–170 hours for males and 210–221 hours for females. The large number of metabolites identified in the excreta showed that desulfinyl fipronil was metabolised extensively by oxidation and hydrolysis, as well as sulfate, glucuronide and glutathione conjugation (Totis 1996).

Percutaneous absorption

In a dermal absorption study in rats, [$^{14}$C]-MB 46513 (desulfinyl fipronil) was applied to shaved intact skin under non-occlusive dressings at concentrations of 0.8, 8.1 or 80.3% (w/v) in 1% carboxymethylcellulose for intervals of up to 24 hours. At 0.8% and 8.1% MB 46513 (fipronil desulfinyl) respectively, 2.6% and 0.35% of the radioactivity was absorbed systemically over 24 hours, with a total absorption of 9.3% and 1.7% respectively when radioactivity retained at the application site was also included. For the 80% group, the application site appeared to become saturated early in the experiment, reaching a maximum total absorption (systemic absorption + radioactivity at the application site) of about 0.7% of the applied dose at 4 hours post-application (Cheng 1996).

Short-term repeat-dose studies

In a preliminary 28-day study, mice received MB 46513 (desulfinyl fipronil) in the diet at 0, 0.5, 3, 30 or 60 ppm, equal to (male/female) 0/0, 0.08/0.10, 0.49/0.61, 5.02/5.65 and 7.05/12.1 mg/kg bw/day respectively. Deaths occurred at 30 and 60 ppm, more so in males, along with clinical signs of increased motor activity, excessive jumps, irritability to touch and compulsive biting. Body weight gain was reduced in these groups, associated with reduced food consumption, particularly in males. Liver weight relative to bodyweight was increased in 30-ppm males and 60-ppm females, along with microscopic changes (centrilobular hypertrophy) in some instances. The NOEL was 3 ppm (equal to 0.5 mg/kg bw/day), based on treatment-induced clinical signs and deaths, reduced bodyweight gain, as well as increased relative liver weight and microscopic changes to the liver at 5 mg/kg bw/day (Dange 1994b).

In a 14-day gavage study, 5 rats/group were dosed with MB 46513 (fipronil desulfinyl) at 0, 0.3, 1, 3, or 10 mg/kg bw/day. One 3 mg/kg bw/day female died, and all rats at 10 mg/kg bw/day died or were killed moribund on days 5–8. Some animals had convulsions prior to death, and clinical signs (piloerection, chromodachryorrhea, prostration, excessive reaction to noise, curled up at handling, hunched posture, nasal discharge and few faeces) were noted at ≥3 mg/kg bw/day. Also at these doses, food consumption and bodyweight gain were reduced, and at 3 mg/kg bw/day, total bilirubin was decreased. No effects were observed at 1 mg/kg bw/day (Dange 1994c).

Rats received MB 46513 (desulfinyl fipronil) in the diet for 28 days at 0, 0.5, 3, 30 or 100 ppm, equal to (male/female) 0/0, 0.04/0.04, 0.23/0.24, 2.20/2.32 and 3.74/3.80 mg/kg bw/day respectively. One 30-ppm male died on day 6, and all 100-ppm rats died (days 5-15). One 100-ppm rat had tonic/clonic convulsions prior to death; and other clinical signs (piloerection, appeared thin, emaciation, excessive vocalisation and curled up at handling) occurred at ≥30 ppm. Also at these doses, food consumption and bodyweight were decreased, T3 and T4 levels were reduced (changes in T3 only in 100 ppm females), and total bilirubin was lower than controls at 30 ppm. No effects were observed at 3 ppm (equal to 0.23 mg/kg bw/day) (Dange 1995a).

In a 28-day study, dogs were administered MB 46513 (desulfinyl fipronil) in the diet at 0, 27, 80 or 270 ppm. At 270 ppm, the dogs were sacrificed on day 10 due to lack of food consumption. The 80 ppm animals were sacrificed moribund on days 10 or 15. There were no deaths at 27 ppm. Food consumption at 27 ppm was equal to 1 mg/kg bw/day, and at 80 and 270 ppm during week 1, dogs consumed (male/female) 1.9/1.7 and 2.3/2.3 mg/kg bw/day respectively, with much lower consumption in week 2, which was associated with weight loss. One animal at 27 ppm had clonic convulsions just prior to scheduled sacrifice. Neurotoxic effects were also seen at higher doses, with reduced motor activity, staggering step, irritability, increased salivation, absence of or few faeces, and emaciation observed at 80 ppm, and emaciation and few faeces at 270 ppm. At 80 ppm, inflammatory and degenerative changes were seen in the liver, and thymic atrophy, red foci on the lungs and black spots on the gastric mucosa were also observed. A NOEL was not established in this study due to clonic convulsions at the lowest dose, equal to 1 mg/kg bw/day (Dange 1995b).

Subchronic studies

Mice were fed 0, 0.5, 2 or 10 ppm MB 46513 (desulfinyl fipronil) in the diet for 90 days, equal to (male/female) 0/0, 0.08/0.11, 0.32/0.43 and 1.74/2.15 mg/kg bw/day respectively. At 10 ppm, one female died on day 5, nine males died on days 20-62, and one male was killed moribund on day 84. Aggression and irritability to touch were observed in two male mice at 2 ppm, and one at 10 ppm, but due to the high death rate, and similar signs in other studies, the effects at 2 ppm could not be dismissed. The livers of some decedent males showed enlargement and/or mild centrilobular hypertrophy, or hepatocellular mitotic figures. The NOEL was 0.5 ppm (equal to 0.08 mg/kg bw/day), based on clinical signs of aggression and irritability to touch at 0.3 mg/kg bw/day (Bigot 1996).

In a 90-day study, rats received MB 46513 (desulfinyl fipronil) in the diet at 0, 0.5, 3, 10 or 30 ppm, equal to (male/female) 0/0, 0.03/0.04, 0.18/0.21, 0.59/0.71 and 1.8/2.1 mg/kg bw/day, respectively. One moribund male was killed on day 45, and three females died (days 11, 13 or 64). Clinical signs of aggression, irritability to touch and excessive vocalisation were observed in the 10 and 30 ppm groups, mainly in weeks 3–5, and occasionally in one male at 3 ppm. Bodyweight gain was reduced in 10 and 30 ppm rats of both sexes, though only slightly in the 10-ppm females. Food consumption was reduced at 30 ppm early in the study.

Bilirubin and cholesterol levels were lower than controls in 30-ppm females, with slight reductions in T3 and/or T4 levels in both sexes at this dose. A macroscopic examination of the rats that died prior to scheduled sacrifice revealed that adrenals were enlarged in all animals, necrotic areas were present in the livers of two females, and focal gastric ulcerations/erosions were present in the male and one of the females. The NOEL was 3 ppm (equal to 0.18 mg/kg bw/day), based on treatment related clinical signs and reduced bodyweight gain at 0.6 mg/kg bw/day (Dange 1994d).

Dogs were fed diets containing MB 46513 (desulfinyl fipronil) at 0, 3.5, 9.5 or 35 ppm for 90 days, equal to (male/female) 0/0, 0.1/0.1, 0.27/0.29 and 0.95/1.05 mg/kg bw/day respectively. One 35-ppm female was killed on day 28, exhibiting increased salivation, prostration, writhing, tremors, absence of rotular reflex, noisy breathing and dyspnoea. Necropsy revealed marked coronary arteritis and myocardial necrosis. Another female at this dose displayed excessive barking and aggressiveness on day 28 and salivation, irritability and tremors on day 86. Mean bodyweights and food consumption were comparable between groups. Gross and microscopic examination of various tissues revealed no changes considered to be treatment related. Based on the clinical signs seen in females at 35 ppm (equal to 1.05 mg/kg bw/day), the NOEL was 9.5 ppm (equal to 0.27 mg/kg bw/day) (Dange 1996).

Chronic study

In a two-year combined chronic/carcinogenicity study, MB 46513 (desulfinyl fipronil) was administered to rats in the diet at 0, 0.5, 2 or 10 ppm. As a result of increased mortality rates being observed by study week 26, the dose for 10-ppm females was reduced to 6 ppm. In ascending order, doses were equal to (male/female) 0/0, 0.025/0.032, 0.098/0.127 and 0.497/0.546 mg/kg bw/day. Overall, the mortality rate was increased in all treated groups of both sexes, but it was considered possibly related to treatment only in females at ≥2 ppm. An increased incidence in the clinical signs of aggressiveness and irritability was considered treatment-related in males at ≥2 ppm. Convulsions were seen in all groups, though this was considered to be related to treatment only in females at ≥2 ppm. The incidence of spongiosis hepaticus was increased in males at ≥2 ppm, but as this was similar to the control incidence in a separate concurrent study, it was considered incidental to treatment. There were no neoplastic findings that could be attributed to treatment. The NOEL was 0.5 ppm (equal to 0.03 mg/kg bw/day), based on increased mortality and convulsions in females at 2 ppm (equal to 0.1 mg/kg bw/day), and an increased incidence of aggressiveness and irritability to touch in males at the same dose (equal to 0.12 mg/kg b/w/day) (Bigot 1998).

Developmental

In a developmental study, MB 46513 (desulfinyl fipronil) was administered to rats by gavage at 0, 0.2, 1.0 or 2.5 mg/kg bw/day during gestation days 6 to 15. Maternal bodyweight gain was reduced at 2.5 mg/kg bw/day in conjunction with reduced food consumption. The incidence of maternal hair loss, sometimes severe, was also increased at this dose. Fused placentas were noted for one dam at 1 mg/kg bw/day and three dams at 2.5 mg/kg bw/day, but no associated adverse effects on the foetuses were apparent. Foetal bodyweight was reduced at 2.5 mg/kg bw/day, and this was associated with slightly delayed ossification of various bones, but no foetal abnormalities were observed. The NOEL for maternal toxicity was 1 mg/kg bw/day, based on reduced bodyweight gain and severe hair loss at 2.5 mg/kg bw/day. The NOEL for embryo-foetal developmental toxicity was 1 mg/kg bw/day, based on delayed skeletal ossification at doses of 2.5 mg/kg bw/day (Foulon 1997).

Neurotoxicity

In an acute neurotoxicity test, rats were given single doses of MB 46513 (desulfinyl fipronil) at 0, 0.5, 2 or 12 mg/kg bw by gavage, then observed for 14 days. A functional observation battery (FOB) and motor activity assessment were performed on all animals before treatment, at 6 hours post-dosing, and on days 7 and 14. In a dose range-finding study, the time of peak effect was determined to be 4 to 6 hours after dosing. In the main study, no unscheduled deaths occurred. A significantly lower bodyweight gain was reported for both sexes at 12 mg/kg bw over the first week, and this was a consequence of significantly decreased food consumption for both sexes at this dose. Bodyweight gains recovered by study week 2, and in some animals, the rate slightly exceeded controls at this time. Bodyweight gains were unaffected at lower doses, and final mean bodyweights were comparable for all groups. In the FOBs, both sexes receiving 12 mg/kg bw/day showed treatment-related decreased footsplay, decreased locomotor activity and lower rectal temperature at 6 hours, and increased incidences of slow righting reflex (males only) on days 7 and 14. There were no significant differences in brain weights or measurements, and slight increases in axonal degeneration at 12 mg/kg bw were not considered toxicologically significant. The no-effect level in this study was 2 mg/kg bw, based on decreased bodyweight gain in the first week after treatment, and findings in the FOB tests (decreased footsplay, drop in rectal temperature, slow righting reflex, decreased locomotor activity) at 12 mg/kg bw (Hughes 1996).

### *MB 45950 (fipronil sulfide)*

In a preliminary study, dogs were treated orally with 0, 1, 5 or 15 mg/kg bw/day of MB 45950 (fipronil sulfide) in gelatin capsules for 28 days. There were no deaths or treatment-related clinical signs. At 15 mg/kg bw/day, female bodyweight gain was reduced, associated with reduced food consumption in half of these animals. Also at this dose, females had slightly increased haematocrit, haemoglobin and red blood cell numbers, while ALP activity was increased in males. The NOEL was 5 mg/kg bw/day (Broadmeadow 1991a).

MB 45950 (fipronil sulfide) was administered to rats in the diet at 0, 10, 25, 50 or 300 ppm, equal to 0, 0.7/0.8, 1.8/2.2, 3.5/4.1, 21.5/24.6 mg/kg bw/day for males/females respectively, for 13 weeks. There were no deaths. At 300 ppm, damaged vibrissae and nasal (discharge) staining were noted. Food consumption was reduced in week 1, and overall bodyweight gain was reduced in males. Absolute and relative liver and thyroid weights were increased at 50 and 300 ppm in both sexes, with liver weights also increased in 25 ppm females. In both sexes, the incidences of thyroid follicular cell hypertrophy and hyperplasia were increased at 300 ppm, with findings of hypertrophy in 1 or 2 animals at 50 ppm, and 1 male at 25 ppm. The NOEL was 10 ppm, (equal to 0.7 mg/kg bw/day) based on increased liver weight in females and thyroid follicular cell hypertrophy in one male at 25 ppm (equal to 1.8 mg/kg bw/day) (Broadmeadow 1991b).

### *RPA 200766 (fipronil amide)*

The fipronil metabolite RPA 200766 (fipronil amide) was administered to rats in the diet for 28 days at 0, 50, 500, 5000 or 15000 ppm, equal to 0, 3.8/4.4, 38/44, 385/387 or 1087/1063 mg/kg bw/day, respectively, for males/females. One 15,000 ppm female died. Bodyweight gain was reduced at ≥5000 ppm, and this was associated with decreased food consumption. At ≥5000 ppm, urea was increased in females and creatinine was increased in males, along with an increase in urine volume in males at ≥5000 ppm and in females at 15,000 ppm indicating renal toxicity. In both sexes, cholesterol was increased at ≥500 ppm and triglycerides

were increased at ≥5000 ppm, while total protein was increased in males at 15,000 ppm, indicative of toxic effects on the liver. Liver weights were increased at ≥500 ppm, and hepatocellular hypertrophy was seen at 5000 ppm. Thyroid and prostate weights were increased in males at ≥500 ppm. Adrenal weights were increased in all treated male groups, accompanied by extra-medullary haemopoiesis at 5000 ppm, and fine/coarse vacuolation of the zona fasciculata at all doses in males and in 5000-ppm females. Because of increased adrenal weights and microscopic changes to this organ in all male groups, a NOEL was not established in this study. The Lowest Observed Effect Level (LOEL) was 4 mg/kg bw/day (Berthe 1996).

### *RPA 104615 (fipronil detrifluoromethyl sulfonate)*

Rats were treated with RPA 104615 (fipronil detrifluoromethyl sulfonate) in the diet for 28 days at 0, 50, 500, 5000 or 10000 ppm (equal to 0, 4.5/4.7, 45.7/50.4, 458/487 and 916/950 mg/kg bw/day for males/females, respectively). At ≥5000 ppm, prothrombin times were increased in males, triglycerides were increased in females, and plasma ALP was increased in both sexes. Total cholesterol was increased in females at 10,000 ppm, and urinary pH was increased in all treated male groups, though in the absence of related findings, the latter was not considered toxicologically significant. Liver weights were increased at ≥5000 ppm, and there was an increased incidence of apparent hypertrophy of the follicular epithelium in the thyroid of males at 10,000 ppm. The NOEL was 500 ppm (equal to 45 mg/kg bw/day) based on liver toxicity (increases in liver weights, plasma ALP and triglyceride levels, and prothrombin times) at 5000 ppm, which is equal to 460 mg/kg bw/day (Dange 1998).

### *MB 45897/RPA 097920 (fipronil detrifluoromethylsulfinyl)*

Rats were dosed with RPA 097920 (fipronil detrifluoromethylsulfinyl) at 0, 50, 200 or 1000 mg/kg bw/day in maize oil by gavage for four weeks. Hunched posture and hypoactivity were observed at ≥200 mg/kg bw/day, with fur loss at 1000 mg/kg bw/day. Bodyweight gain was reduced in males at 1000 mg/kg bw/day. In females at 1000 mg/kg bw/day, red blood cell counts, haemoglobin and haematocrit were slightly lower than controls. Total protein was increased in both sexes at 1000 mg/kg bw/day, along with alpha-2-globulins, beta-globulins and/or albumin. Lower levels of potassium and chloride and higher urea levels were observed in males of this group. Absolute and relative liver weights were increased at 1000 mg/kg bw/day in both sexes, associated with periacinar hepatic hypertrophy in some animals. The NOEL was 200 mg/kg bw/day, based on changes in haematology, clinical chemistry, and increased liver weight with associated pathological changes at 1000 mg/kg bw/day (Johnson 1995).

## HUMAN STUDIES

### *Case studies*

In a case study involving a worker who had sprayed Regent 200 SC (dilution not provided) for 5 hours without wearing any personal protection equipment, headache, nausea, vertigo and weakness were reported, commencing 2 hours after completion of the spraying operation, and resolving spontaneously after 5 hours. Physical and biochemical examinations were normal, but the interpretation of symptoms was confounded by the patient's history of heart disease (Chodorowski and Anand 2004).

Mohamed et al. (2004) reviewed seven prospectively recorded cases of self-poisoning with the fipronil product Regent 50 SC, sometimes ingested with other pesticides and/or alcohol. One patient who had ingested 100 mL of the fipronil product was admitted to hospital unconscious, whereupon he experienced

several episodes of epileptic fits, subsequently developed pneumonia, and after 17 days without regaining consciousness, died. For the other cases overall, fipronil poisoning was characterised by vomiting, agitation and seizures. The outcome was normally favourable if resuscitation and supportive care were provided. This study indicated that fipronil is rapidly absorbed in humans, with clinical toxicity peaking in the first few hours and correlating with blood levels of fipronil and its metabolites. In two patients there was sufficient information to estimate an elimination half-life of 36–47 hours.

### *Exposure studies – dog and cat stroking studies*

Studies were conducted to quantify the fipronil residues that can be dislodged by stroking the coat of a cat or dog treated with either Frontline Top Spot (10% fipronil) or Frontline Spray (0.25% fipronil) when used according to label instructions. Samples were collected from cotton gloves worn by the experimenter. Sampling occurred on three occasions on the day of treatment, then on a number of days up to day 29 post-treatment, from cats and medium dogs treated with the spot-on formulation (0.5 mL or 1.34 mL), or with the spray (6 mL/kg bw). Where detectable, fipronil sulfone and fipronil sulfide were found at very low levels relative to the parent compound, but desulfinyl fipronil was not detected. In nearly all cases, fipronil dislodgeable residues were detected throughout the study period, with maximum levels on the day of application, except for the spot-on treatment of dogs, where the time of maximum residue levels varied between days 1 to 3. The mean maximum amounts of fipronil residues dislodged after spray application were approximately 300 micrograms (µg) and up to 3 mg for cats and dogs respectively. For the spot-on, mean levels were up to approximately 7 mg on cats stroked at 1 hour post-application, or 1 mg if left for 4 hours, and for dogs up to approximately 4 mg was dislodged (Hughes 1997b,c,d,e; de Fontenay 1997a,b,c,d).

The amount of fipronil residues that could be dislodged when human hands vigorously contacted a dog treated with Frontline Spot On (1.34 mL; 10% fipronil) was measured. Maximum dislodgeable residues were detected at 1 day post-application, approximately equivalent to 2.4 mg fipronil, decreasing to about half this level after three weeks, with little remaining at day 29, and none detectable on day 36 (Jennings 2002).

In a study to evaluate the presence of desulfinyl fipronil on dog hair after treatment of the animal with Frontline spot-on or spray formulations, dogs were allowed access to outside natural light for approximately 6 hours a day on weekdays and 3 hours a day on weekends/holidays for a period of 4 weeks. The outermost section of hairs removed from the backs of dogs treated with the spot-on had desulfinyl fipronil levels equivalent to 3.7–6.2% of the total fipronil residues present, increasing over the period from day 3 to day 14 post-application, but below the limit of quantification thereafter. Following treatment with the spray, desulfinyl fipronil residues were maximal on day 3, and detectable up to day 21, representing about 4.5–2.4% of total fipronil over this interval (Astruc et al. 1998).

### *Occupational exposure and indoor air levels following termiticide treatment*

A total of 16 houses were treated by pest control operators with 0.07–0.08% Termidor 80 WG in water at 4.968 L/minute on outer and interior walls and 2.484 L/minute injected into foundation walls. Exposures in 16 of the workers ranged from 0.03 to 5.5 µg/kg/hour, with a mean of 0.95 µg/kg/hour, following application to houses with crawl-spaces. Airborne fipronil residues in treated houses ranged from 0.006–0.081 nanograms per litre (ng/L) in slab-construction houses, 0.005–0.042 ng/L in houses with cellars, and 0.004–0.011 ng/L in houses with crawl-spaces. Airborne fipronil residues were detected most frequently on the day of application,

with residues still detectable in three houses 7 days after application. Airborne fipronil residues were below the limit of detection in four of the 16 treated houses (Honeycutt 2001).

## OTHER STUDIES

### *Mechanism of action*

In a series of *in vitro* experiments, Bushey (1993) demonstrated that fipronil reversed the effect of gamma-aminobutyric acid (GABA) in the central nervous system of housefly maggots, inhibited GABA-activated transport of chloride ions across the cell membrane in rat brain microsomes, and inhibited the GABA-induced electrical response in oocytes expressing the GABA receptor. It was also demonstrated that the fipronil binding site co-localised with the GABA-gated chloride channel in rat brain and insect tissue.

Fipronil was shown to bind strongly *in vitro* to GABA-gated chloride channels in rat and mouse brain. In contrast, the metabolites RPA 200766 (fipronil amide) and RPA 105048 (desulfinyl fipronil amide) showed no activity in binding assays. It was stated that the major fipronil metabolites MB 45950 (fipronil sulfide) and MB 46136 (fipronil sulfone) bind well to the GABA receptor *in vitro*, but data were not provided. These results are consistent with results of assays for GABA-induced chloride ion flux in rat brain membranes, in which fipronil was inhibitory but RPA 200766 (fipronil amide) and RPA 105048 (desulfinyl fipronil amide) were not (Fitzgerald 1993).

### *Blood pressure, heart rat and electrocardiographic studies*

Rabbits received oral doses of 0 or 4 mg/kg bw fipronil. Arterial blood pressure, heart rate and electrocardiograph measurements were recorded before and 1, 24, 48, 72, 96 and 120 hours after dosing. Under the conditions of the study, fipronil did not influence any of these functions, nor were there signs of toxicity (Richard and Camperoux 1990).

### *Electroencephalogram studies*

The cortical EEG was recorded prior to dosing and at 24 hour intervals post-dosing for 1 week, for 30 minutes duration, in two groups of rabbits receiving either a single gavage dose of the vehicle, or 4 mg/kg bw fipronil. Fipronil induced a significant 'right shift' (towards higher frequencies) in the mean and median frequency in the electroencephalogram at 72 hours, with percent total electrical activity also increased at 72, 144 and 168 h. The electroencephalogram waveforms were not considered 'pathological', and the possible slight central nervous system activation was not accompanied by behavioural changes (Algate et al. 1991a).

Two groups of rabbits received daily gavage doses of 4 or 8 mg/kg bw fipronil. The cortical electroencephalogram was recorded prior to the first treatment and at 1 hour post-dosing for the next 4 days. The study was terminated on day 5, following the death of three rabbits (two in the 4 mg/kg bw/day group) from toxic effects. Neurotoxic clinical signs, predominantly tremors, were observed throughout the study period, and both groups of rabbits lost weight. Detailed spectral analysis revealed evidence of possible slight central nervous system (electroencephalogram) activation, which was more notable in the 4 mg/kg bw/day group. The peak effect was at 72 hours (Algate et al. 1991b).

### *Enzyme induction*

The ability of fipronil to induce hepatic microsomal cytochrome P 450 proteins and phase II conjugation enzymes in the mouse, rat and rabbit was investigated following oral gavage administration daily for 4 or 14 days. Doses of 1.2 or 5.0 mg/kg bw/day were administered to rats and mice, and 0.3 or 1.2 mg/kg bw/day to rabbits. A number of mice in each group died (more females than males), and this was preceded by substantial weight loss. Relative liver weight was increased in female rats at doses of 5 mg/kg bw/day for both treatment periods. An associated finding was increased total levels of cytochrome P450 in both sexes after the 4-day treatment, but levels were similar to controls after the corresponding treatment for 14 days. No inductive response was apparent in rabbits, but mice showed an increase in microsomal protein content and associated mixed function oxidase activities after 14 days' dosing. Effects on Phase II enzymes were limited to decreased cytosolic glutathione S-transferase in rats (14 days treatment only), decreased methylumbelliferone glucuronyl transferase activity in male rabbits (after 4 days) and mice (both sexes and both treatment periods), and decreased microsomal glucuronidation of 1-naphthol in mice (after 14 days) (Shavila et al. 1990).

### *Thyroid function tests*

The effect of fipronil on thyroid function was investigated in rats by comparing it with the effect of propylthiouracil (PTU), a known inhibitor of iodide organification in many species, and noxyflex, another thiourea compound that lowers serum thyroxine levels and reduces iodide organification in cultured porcine thyrocytes *in vitro*. A large reduction in the $^{125}$I content of thyroids, and relatively less $^{125}$I radioactivity in the thyroid than in the blood, was observed in PTU-treated animals that had been given perchlorate. Neither noxyflex nor fipronil inhibited iodide organification. Potassium perchlorate did not change blood and thyroid $^{125}$I levels. It was concluded that fipronil and noxyflex enhanced the accumulation of radiolabelled iodide in the thyroid and triggered a stimulation of thyroid activity by a mechanism not involving direct inhibition of iodide organification (Peters 1991).

Rats received fipronil at 0, 0.1, 1, 5 or 30 ppm (equal to 0, 0.01, 0.1, 0.5 and 2.9 mg/kg bw/day) in the diet for four weeks. At 5 ppm, decreases in T3, T4 and/or TSH levels and a marginal increase in thyroid weights were recorded for males only. At 30 ppm, T3 levels fluctuated, T4 levels were reduced and TSH levels were increased. Findings were attributed to an increase in T4 clearance from the blood, resulting in a reduction of the feedback inhibitory control of T4 on thyroid function. At 1 or 0.1 ppm, an effect on T3, T4 or TSH was not established, and there were no compound related organ weight differences or microscopic findings. The no observed effect level was 1 ppm, equivalent to 0.1 mg/kg bw/day (Peters et al. 1991).

Rats were given a single oral dose, or daily doses for 14 days, of fipronil at 0, 1 or 10 mg/kg bw/day, followed by sodium iodide immediately after the last dose, and $^{125}$I-thyroxine (T4) 4 hours later (intravenous). Phenobarbitone was employed as the positive control. Two weeks of treatment with either fipronil or phenobarbitone enhanced biliary clearance of radiolabelled T4. Excretion of T4 conjugated products during 0 to 5 hours increased about threefold with 1 mg/kg bw fipronil, fourfold for 10 mg/kg bw fipronil, and fivefold for phenobarbital. Single doses of fipronil at both levels, and phenobarbital, raised biliary excretion of conjugated $^{125}$I during 0–5 hours by 48–74%. Bile output increased following phenobarbital or 10 mg/kg bw fipronil treatment for 14 days (Chasseaud et al. 1993).

Rats were dosed for 1 or 14 days with fipronil (10 mg/kg bw/day, orally), or phenobarbital (80 mg/kg bw/day, intraperitoneal). Fipronil at 10 mg/kg bw/day for 14 days increased T4 clearance from blood. This was paralleled by a decrease in T4 terminal half-life in blood. After only 1 day of dosing with fipronil (10 mg/kg bw), similar but less marked effects were noted. Phenobarbital produced changes similar to those affected by fipronil at 1 or 14 days post-dosing (Peters 1991).

## 3.1.2 Hazard assessment

### REASONS FOR THE REVIEW

Concerns over human health and animal safety prompted the decision by the APVMA to review fipronil and reconsider the safety of products containing this active constituent to persons using them in agricultural or veterinary situations, and the adequacy of label instructions. These concerns arose from a number of adverse experience reports associated with veterinary products containing fipronil. In these reports, symptoms reported included skin reactions in animals and humans, neurological signs and deaths in target animals (though concurrent infestations with paralysis ticks have been a confounding factor in the latter), and deaths following off-label use in domesticated rabbits. Dermal effects were also reported in humans handling animals with fipronil products and, potentially, constitute the major health concern arising from these adverse experience reports. A critical evaluation of these adverse experience reports is included in this review (see section 3.1.5).

### ADEQUACY OF DATABASE

A range of studies on fipronil and its metabolites were submitted for the review. Taking into account data that have been evaluated previously by the OCSEH, the toxicology package for fipronil and its metabolites and degradates is comprehensive.

However, given the potential concerns that the dermal effects reported in the human adverse experience reports may be associated with the use of veterinary products containing fipronil, and the possibility that exposure to fipronil photodegradates may be the causative agent for these skin reactions, the inclusion of a sensitisation study for the photodegradate desulfinyl fipronil would have been informative.

### MODE OF ACTION

Fipronil belongs to the phenylpyrazole class of insecticides/acaricides, which also contains acetoprole, ethiprole, pyrofluprole, pyriprole and vaniliprole, none of which is registered in Australia. Ethiprole is registered in Japan and an evaluation is available.[1] This compound differs from fipronil in chemical structure by replacement of the trifluoromethylsulfinyl group at the fourth carbon on the pyrazole ring with an ethylsulfinyl moiety. It is much less lipophilic than fipronil, and according to the Japanese evaluation, appears to be relatively less toxic to mammals. In common with fipronil, ethiprole produced thyroid and liver tumours

[1] *Evaluation Report Ethiprole*. Food Safety Commission, Pesticides Expert Committee, 21 July 2004, <http://www.fsc.go.jp/english/ethiprole_fullreport.pdf>.

in rats and mice respectively, but though its mode of action in insects and its potency has been described as similar to fipronil,[2] neurotoxicity was not reported in mammalian studies.

Fipronil acts at the GABA receptor in the central nervous system as a non-competitive blocker of the GABA-gated chloride channel, GABA being the chief inhibitory neurotransmitter in the mammalian brain. The binding of GABA to its receptor allows the passage of chloride ions through the central pore, the consequence of which is hyperpolarisation of the neuron, which decreases the probability that it will propagate an action potential. Blockage of the GABA-gated chloride channel by fipronil reduces neuronal inhibition, which may lead to hyper-excitation of the central nervous system, convulsions and death.

*In vitro* assays have demonstrated that the GABA receptors of insects are more sensitive to the action of fipronil than the analogous receptors in mammals (Bushey 1993; Hainzl 1998). It has also been shown that fipronil may act at the insect L-glutamate-gated chloride channel, which has no known counterpart in the vertebrate nervous system; this provides an additional explanation for the greater toxicity of fipronil in insects relative to mammals.[3] It has been reported that two fipronil metabolites of mammals and plants (fipronil sulfone and fipronil sulfide), and the major photodegradation product (desulfinyl fipronil), act in a similar way to the parent compound at the GABA receptor (Fitzgerald 1993).[4] The toxicity of these fipronil derivatives is discussed in detail below.

## NEUROTOXICITY

In keeping with the mode of action of fipronil outlined above, clinical signs such as tremors, hyperactivity, irritability, aggression, twitching, jerking, gait abnormalities and convulsions were observed in mice, rats, rabbits and dogs across a range of oral studies with fipronil, and in an acute dermal toxicity study in rabbits. Results obtained in an electroencephalogram performed on rabbits treated with fipronil were indicative of slight central nervous system activation (Algate et al. 1991a). However, neurotoxicity studies did not reveal any changes to the histopathology, weight, or dimensions of the brain in these animals (Hughes 1997a; Holmes 1991d).

Convulsions and other clinical signs of neurotoxicity also occurred in mice, rats and dogs treated with fipronil desulfinyl via the oral route. The possible differences in neurotoxicity between desulfinyl fipronil and the parent compound are discussed below. Convulsions were not observed in the limited number of repeat dose (dietary) studies performed with other fipronil metabolites, but were reported in acute toxicity studies using fipronil sulfone, fipronil sulfide and desulfinyl fipronil amide (but not fipronil carboxylic acid, fipronil sulfonyl amide and fipronil detrifluoromethyl sulfonate).

---

[2] Caboni P, Sammelson RE and Casida JE 2003, 'Phenylpyrazole insecticide photochemistry, metabolism and GABAergic action: ethiprole compared with fipronil', *Journal of Agricultural and Food Chemistry* 51:7055–7061.

[3] Zhao X, Yeh JZ, Salgardo VL and Narahashi T 2004, 'Fipronil is a potent open channel blocker of glutamate-activated chloride channels in cockroach neurons', *Journal of Pharmacology and Experimental Therapeutics* 310:192–201.

[4] Hainzl D and Casida JE 1996, 'Fipronil insecticide: Novel photochemical desulfinylation with retention of neurotoxicity', *Proceedings of the National Academy of Sciences, USA*. 93:12764–12767.

## TOXICOKINETICS AND METABOLISM

Following acute oral dosing in rats, the rate at which fipronil appeared in the blood was dependent on dose. At a relatively low dose (4 mg/kg bw), the maximum concentration of radiolabel in the blood was achieved at 4–6 hours after dosing, and was distributed widely in the tissues. At doses of 40 mg/kg bw, absorption was slower, with blood levels peaking at 34–38 hours (Totis and Fisher 1994). Elimination was slow (half-life 135-241 hours) at both 4 and 40 mg/kg bw, and occurred mainly through the faecal (including biliary) route (Totis and Fisher 1994). The results of biliary excretion experiments indicated that fipronil and/or its metabolites in the tissues were released slowly, and mainly via the bile (Totis 1995). Re-uptake of approximately 25% of biliary metabolites was demonstrated, with redistribution of a significant proportion of the re-absorbed metabolites into the tissues, contributing to the extended elimination phase (Kemp 1999). The slow rate of elimination and considerable enterohepatic recirculation indicate the potential for accumulation of fipronil and/or its metabolites in tissues. In support of this, the autoradiographic study shows stores of radioactivity in the fat in rats, rabbits, and mice (Whitby 1991). The urine was a minor route of excretion at a dose of 4 mg/kg bw (about 5% of the dose) but accounted for up to 25% of administered radioactivity at 150 mg/kg bw (Powles 1992). Taking biliary excretion into account, absorption of a single oral dose of fipronil was 80–90% of the administered dose.

Fipronil was readily metabolised, with little or no parent compound detected in the tissues and urine. The highest tissue levels of fipronil and/or its metabolites were found in the fat, with significant levels in the adrenal gland, pancreas, skin, liver, ovaries, uterus, thyroids, kidney, muscle and brain (Totis and Fisher 1994; Kemp 1999). The main metabolite detected in the tissues and excreta was fipronil sulfone, though in the faeces the parent compound and fipronil sulfide were also prominent (Brockelsby et al. 1991; Powles 1992). Fipronil and fipronil sulfone were detected in the brains of mice after dietary fipronil administration for periods of 2 to 4 weeks at about 10–20 mg/kg bw/day, demonstrating that the parent compound and its major metabolite crossed the blood brain barrier (Fisher 1991,1992). The range and type of metabolites in the bile was indicative of extensive metabolism prior to excretion by this route (Totis 1995).

No sex differences were detected in the toxicokinetics of fipronil or its metabolism, but interspecies differences were apparent. *In vitro* studies showed that rabbit hepatocytes metabolised fipronil at approximately half the rate of rat hepatocytes, but both produced the same metabolite: fipronil sulfone (Fisher 1992; Guyomard 1993). *In vivo* studies found that fipronil sulfone was eliminated more slowly in rabbits than it was in rats and mice, with relatively high levels of this metabolite persisting in rabbit tissues, particularly in the fat (Brockelsby 1991). In an *in vitro* study, human microsomes also metabolised fipronil to fipronil sulfone, though the metabolism rates varied widely (by a factor of about forty-fold) within the pool of donors (Tang et al. 2004). Overall, the available evidence suggests that metabolism of fipronil is qualitatively similar across laboratory mammalian species. The slow metabolism and elimination of fipronil in rabbits may at least partially explain why this species appears to be more sensitive to the effects of fipronil than other species (e.g. King 1990; Myers and Christopher 1992).

## PERCUTANEOUS ABSORPTION

In rats, dermal absorption of fipronil was low (<1%), but greater amounts (up to about 6%) were found in the skin at the application site (Cheng 1995). There was insufficient information in this study to determine whether the fipronil reservoir in the skin subsequently entered the systemic circulation. As fipronil and/or its metabolites are expected to accumulate in the tissues following repeated exposure, it is reasonable to

consider that fipronil in the skin was available for systemic absorption. In that case, the maximum amount of the applied dose that could be absorbed is approximately 7% (Cheng 1995). *In vitro* studies under the same laboratory conditions indicated that rat skin was slightly over 10 times more permeable to fipronil than human skin was (Walters and Brain 1990; Ward 1997a,b, 1998). Therefore, taking into account the tenfold difference in permeation between rat and human skin, and allowing for the fipronil found in the skin to be absorbed systemically, it is reasonable to apply a dermal absorption factor of 1% to exposure scenarios for which an oral to dermal extrapolation is required for human risk assessment. If a single dermal exposure were being considered, it would be acceptable to take into account only the fipronil that entered the systemic circulation.

Like the parent, dermal absorption of the photodegradate desulfinyl fipronil *in vivo* in rats was also low (Cheng 1996). As for fipronil, amounts of desulfinyl fipronil that remained associated with the application site following washing were greater than those absorbed, and were of a similar magnitude. No *in vitro* studies were provided to facilitate the calculation of the likely dermal permeation of desulfinyl fipronil in humans relative to rats. However, given the similarity in molecular structure of fipronil and desulfinyl fipronil, and their similar behaviour in rat *in vivo* dermal absorption studies, it is considered reasonable to assume that they will be dermally absorbed in humans to a similar extent.

## ACUTE TOXICITY OF THE TECHNICAL ACTIVE

Acute oral exposure to fipronil resulted in a rapid onset of clinical signs of neurotoxicity, with deaths occurring in rats and mice at ≥80 mg/kg bw and ≥50 mg/kg bw respectively from 4 hours to within a week of dosing (Gardner 1988a; Mondot and Dange 1995). The oral $LD_{50}$ values were similar in rats and mice (about 90 to 100 mg/kg bw), though different vehicles were used, and it is unclear whether vehicle plays a role in fipronil toxicity. In the toxicokinetic study of Powles (1992), rats were dosed at 150 mg/kg bw using an aqueous vehicle, with no deaths reported, so it is possible that fipronil is more toxic when administered in corn oil, as was the case in the rat acute oral study. It is also possible that the choice of vehicle influenced the relative acute dermal toxicity of fipronil in rats and rabbits, though the differences in metabolism of fipronil between these species, as discussed above, may also play a role. When administered in water by the dermal route, fipronil showed low toxicity in rats, with no toxic effects observed after 24 hours' exposure at 2000 mg/kg bw (Gardner 1988b). Given the poor solubility of fipronil in water (about 2 mg/L), little of this dose would be expected to have been available for absorption. On the other hand, fipronil in corn oil had moderate dermal toxicity in rabbits ($LD_{50}$ values of 445/354 mg/kg bw for males/females), with severe clinical signs of neurotoxicity, including convulsions, at 250 mg/kg bw and above (Myers and Christopher 1992). The flux penetrance of fipronil through rat and rabbit skin *in vitro* was similar when measured under the same experimental conditions (Walters and Brain 1990). Inhalation of fipronil dust resulted in moderate acute toxicity in rats ($LD_{50}$ values of 360–680 mg/$m^3$), again with clinical signs mainly consistent with neurotoxicity (Cracknell 1991; Nachreiner 1995).

The skin irritation potential of fipronil was tested in two separate rabbit studies, one in which the fipronil was applied semi-occluded under a gauze pad moistened with water, and the other in corn oil under an occlusive dressing (Liggett 1988b, Myers and Christopher 1993). The latter study indicated that fipronil was a slight skin irritant, whereas the former reported no reactions. The effect of the different protocols on the outcomes of these studies is not known, but given that skin irritation was observed in 6 out of 6 rabbits in the Myers and Christopher (1993) study, compared to the 3 out of 3 rabbits showing no irritation in the other study, it is concluded that fipronil is a slight skin irritant. Results of two eye irritation studies were also conflicting.

Conjunctival irritation persisted beyond 72 hours for half the animals in one study (resolving by 14 days), along with 'minor transient corneal opacity' and iritis (Myers and Christopher 1993b), but reactions in the other study were limited to slight conjunctival effects that had all resolved by 72 hours, with no effects on the cornea or iris (Liggett 1988). As the term 'corneal opacity' was used to describe a change that was apparent at 1 hour and not thereafter, this is not considered to represent the type of change that would normally be interpreted as moderate irritation. Taking this into account, on the basis of these two studies, fipronil is a slight eye irritant.

When tested for skin sensitisation in guinea pigs by the maximisation test of Magnusson and Kligman (Johnson 1993), although skin reactions were seen in test animals they were considered irritant in nature. Therefore, this study provided no reliable evidence that fipronil is a skin sensitiser in guinea pigs. Furthermore, a negative result was also obtained in another dermal skin sensitisation study in guinea pigs, this time using the Buehler method (Smith 1990). Although some adverse experience reports have reported dermal reactions occurring in humans following exposure to veterinary products containing fipronil, which may potentially be allergic in nature, expert opinion is that this data does not reliably demonstrate that fipronil is a skin sensitiser. This issue is discussed further in Section 3.1.5.

### TOXICITY OF METABOLITES AND PHOTODEGRADATES

There are several metabolites or photodegradation products of fipronil that are of toxicological concern. An extensive database exists for the major photodegradate, desulfinyl fipronil, which, along with another photodegradation product, fipronil detrifluoromethyl sulfonate, has not been identified as a metabolite in mammals. For this reason, and in conjunction with its relatively high toxicity (oral $LD_{50}$ = 18/15 mg/kg bw in male/female rats, Dange 1993a), and its presence as a residue in crops, desulfinyl fipronil is of particular interest for this review. On the other hand, fipronil detrifluoromethyl sulfonate has been shown to have low acute toxicity (oral $LD_{50}$ >2000 mg/kg bw in rats, Dange 1993c), and therefore is not of toxicological concern.

The toxicity of metabolites and photodegradates of fipronil is summarised in Table 2. There is evidence that desulfinyl fipronil may be more acutely toxic than fipronil at their respective $LD_{50}$ values, and in a short-term and a subchronic dietary study. However, effects occurred at similar doses of fipronil and desulfinyl fipronil following chronic treatment in developmental studies and in acute neurotoxicity studies. Overall, it is not clear why desulfinyl fipronil was relatively more toxic than the parent compound in some studies but not in others. Like fipronil, desulfinyl fipronil was widely distributed in the tissues following oral dosing, with the highest concentrations in the fat, and elimination was slow, with faeces the preferred excretory route (though the contribution of biliary secretion is not known for the desulfinyl derivative). The following is a detailed comparison of the toxicity of fipronil and desulfinyl fipronil.

Desulfinyl fipronil had a lower oral $LD_{50}$ in rats than did fipronil (18/15 mg/kg bw vs. 92/103 mg/kg bw for males/females; Dange 1993a; Gardner 1988a). However, in acute neurotoxicity studies performed at doses below their respective $LD_{50}$ values, the NOELs were similar for these two compounds (about 2 mg/kg bw; neurobehavioural effects) (Hughes 1996, 1997a). NOELs were not achieved for fipronil in the rat and mouse short-term oral dosing studies, and the LOELs in these studies were well above the NOELs in the corresponding studies with desulfinyl fipronil (Holmes 1990; Peters et al. 1990; Dange 1994b,1995a). In the mouse short term studies, effects on the liver and reduced bodyweight gain were seen at similar doses for both compounds (2.4 or 5 mg/kg bw/day), but neurobehavioural changes that were seen from 5 mg/kg bw/day for desulfinyl fipronil occurred in one fipronil-treated mouse at about 6 mg/kg bw/day, but

mainly at ≥20 mg/kg bw/day, suggesting that desulfinyl fipronil was relatively more neurotoxic in this instance. This is supported by results from *in vitro* binding studies using mouse brain membranes, in which the GABA receptor $IC_{50}$ values were 97±4 nM for desulfinyl fipronil, 1010 ± 20 nM for fipronil, and >10,000 nM for detrifluoromethylsulfinyl fipronil.[5] Short-term dosing with desulfinyl fipronil proved to be lethal for one male rat at 2.2 mg/kg bw/day and all rats at 3.7 mg/kg bw/day, whereas in comparison only one female rat died at the highest dose tested (about 55 mg/kg bw/day fipronil) in the short-term study. Given the lack of accompanying clinical signs or abnormal pathology findings, this death may not have been treatment-related. In the four-week dog study with desulfinyl fipronil, clonic convulsions were seen at 1 mg/kg bw/day, but no effects were noted at this dose in the corresponding fipronil study, with a possible convulsive episode in one dog at 10 mg/kg bw/day (Dange 1995b; Holmes 1991a).

In the 13-week rat dietary study with desulfinyl fipronil, clinical signs were seen occasionally in one male at 0.18 mg/kg bw/day (Dange 1994d). As the same signs (aggression, irritability to touch and excessive vocalisation) were seen also at the higher doses, this could not be dismissed as unrelated to treatment. In the chronic study performed with desulfinyl fipronil, similar signs were not seen in animals at a comparable dose level during, and for some time after, the treatment period corresponding to the subchronic study, but these rats were a different strain and from a different source, which may account for this (Bigot 1998). Taking dose choices into account, and not placing undue weight on the one finding at the LOEL in the desulfinyl fipronil study, which may represent a threshold effect, it is reasonable to conclude that the fipronil and desulfinyl fipronil are of similar toxicity when administered subchronically in the diet. Fipronil and desulfinyl fipronil were also similarly toxic in the respective chronic rat studies (Aughton 1993; Bigot 1998).

A comparison of the rat developmental studies suggests that desulfinyl fipronil was more toxic than fipronil, as foetal developmental delays and reduced bodyweight were apparent at 2.5 mg/kg bw/day (NOEL 1 mg/kg bw/day) desulfinyl fipronil, but no foetal effects were seen at 20 mg/kg bw/day fipronil (Foulon 1997; Brooker and John 1991). Also, maternal bodyweight loss occurred at 2.5 mg/kg bw/day of desulfinyl fipronil, below the maternal NOEL of 4 mg/kg bw/day for fipronil. However, results are not consistent between the fipronil developmental and developmental neurotoxicity studies (Mandella 1995). Though dosing was over a longer period in the latter, maternal bodyweight gain was reduced during gestation, with a NOEL of 0.9 mg/kg bw/day, equivalent to the same endpoint in the desulfinyl fipronil developmental study. The pup data in the fipronil developmental neurotoxicity study are not directly comparable with results for foetuses in the desulfinyl fipronil developmental study, but if it is accepted that 0.9 mg/kg bw/day represents a threshold dose for reduced pup weight in the neurotoxicity study, then at least this is consistent with the NOEL for foetal effects for desulfinyl fipronil. Therefore, when these three studies are considered together, there is sufficient evidence that desulfinyl fipronil is not more toxic than fipronil in this context.

The primary metabolites of fipronil identified in mammals are fipronil sulfide, fipronil sulfone (the major metabolite found in mammals) and fipronil amide. The oral $LD_{50}$ values for these compounds were respectively 69/100, 184/257 and more than 2000 mg/kg bw for males/females when administered to rats in corn oil. For fipronil sulfone, the $LD_{50}$ was increased to 464/732 mg/kg bw when administered in an aqueous

[5] Hainzl D, Casida JE 1996, 'Fipronil insecticide: Novel photochemical desulfinylation with retention of neurotoxicity', *Proceedings of the National Academy of Sciences, USA* 93: 12764–12767

vehicle. As well as being the most acutely toxic of the derivatives of fipronil for which there are data, the desulfinyl, sulfide and sulfone products also show relatively high affinity for a specific site on the GABA receptor, as assessed by binding assays in competition with radiolabelled EBOB (4'-ethynyl-4-n-[2,3-3H2]propylbicycloorthobenzoate) and TBPS (tert-butylbicyclo-phosphoro-thionate), both of which are known to bind within the GABA-gated chloride channel. Fipronil and its sulfone and desulfinyl derivatives have been shown to inhibit EBOB binding *in vitro* in human brain tissue at $IC_{50}$ values of approximately 942, 155 and 64 nM respectively.[6] It has been reported elsewhere that the sulfone and sulfide metabolites of fipronil exhibit good binding activity, but fipronil amide and desulfinyl fipronil amide do not (Fitzgerald 1993). Except for fipronil sulfone, a correlation generally exists between the ability of the compound to compete with EBOB for binding to the mammalian GABA receptor *in vitro*, and its *in vivo* toxicity in mammals. Fipronil sulfone has greater affinity for the GABA receptor than does fipronil, yet its oral $LD_{50}$ in rats is about twice that of fipronil. Other selected metabolites/degradates tested had oral $LD_{50}$ values of >2000 mg/kg bw, with the exception of desulfinyl fipronil amide, a metabolite of fipronil desulfinyl in rats, which had an oral $LD_{50}$ of 467 mg/kg bw.

Many of the clinical signs observed after acute dosing with the sulfone or sulfide metabolites were similar to those for fipronil, which is consistent with their affinity for the GABA receptor as described above. Most of the metabolites/degradates tested had low acute dermal toxicity in rats ($LD_{50}$>2000 mg/kg bw), though fipronil sulfide was only tested at 500 mg/kg bw, at which dose no effects were observed. In rabbits, fipronil sulfone and fipronil sulfide were slight eye irritants, but were not skin irritants.

**Table 2: Comparison of the toxicity of fipronil and its metabolites/degradation products**

| COMPOUND | $LD_{50}$ ORAL (mg/kg bw) MALES/FEMALES (COMBINED) | $LD_{50}$ DERMAL (mg/kg bw) | REFERENCE |
|---|---|---|---|
| ACUTE $LD_{50}$ STUDIES (RAT) | | | |
| Fipronil | (97) | >2000 | Gardner (1988a) |
| MB 46513 (desulfinyl fipronil) | 18/15 | >2000 | Dange (1993A) |
| MB 45950 (fipronil sulfide) | 69/100 (83) | >500 | Dange (1994a) |
| MB 46136(fipronil sulfone) | 184/257 (218) | >2000 | Gardner (1988c) |
| RPA 200766(fipronil amide) | >2000 | ND | Dange (1993d) |
| RPA 104615 (fipronil detrifluoromethyl sulfonate) | >2000 | ND | Dange (1993c) |
| RPA 105048 (desulfinyl fipronil amide) | 467 | ND | Dange (1994f) |
| RPA 200761 (fipronil carboxylic acid) | >2000 | ND | Katchadourian (1995) |

[6] Hainzl D, Cole LM, Casida JE 1998, 'Mechanisms for selective toxicity of fipronil insecticide and its sulfone metabolite and desulfinyl photoproduct', *Chemical Research in Toxicology* 11:1529–1535.

| COMPOUND | $LD_{50}$ ORAL (mg/kg bw) MALES/FEMALES (COMBINED) | $LD_{50}$ DERMAL (mg/kg bw) | REFERENCE |
|---|---|---|---|
| RPA 105320 (fipronil sulfonyl amide) | >2000 | ND | Dange (1994c) |

| COMPOUND | NOEL (mg/kg bw) | LOEL (mg/kg bw) | ENDPOINT | REFERENCE |
|---|---|---|---|---|
| ACUTE NEUROTOXICITY STUDIES (RAT) | | | | |
| Fipronil | 2.5 | 7.5 | Reduced footsplay | Hughes (1997); Gill (1993) |
| MB 46513 (desulfinyl fipronil) | 2 | 12 | Reduced footsplay, slow righting reflex, decreased locomotor activity, drop in rectal temperature | Hughes 1996 |
| SHORT-TERM REPEAT-DOSE STUDIES (MOUSE) | | | | |
| Fipronil | - | 2.4 | Decreased bodyweight (males); increased liver weight + pathology | Holmes (1990) |
| MB 46513 (desulfinyl fipronil) | 0.5 | 5 | Clinical signs, death, reduced bw gain; increased liver weight + microscopic changes | Dange (1994b) |
| SHORT-TERM REPEAT-DOSE STUDIES (RAT) | | | | |
| Fipronil | - | 3.4 | Increased liver weights; thyroid follicular hypertrophy | Peters et al. (1990) |
| MB 46513 (desulfinyl fipronil) | 0.23 | 2.2 | Decreased bw; decreased T3 and T4 and total bilirubin | Dange (1995a) |
| RPA 200766 (fipronil amide) | - | 3.8 | Clinical signs; reduced bw | Dange (1994d) |
| RPA 104615 (fipronil detrifluoromethyl sulfonate) | 45 | 460 | Increased liver weight; increased ALP, triglycerides, prothrombin time | Dange (1998) |
| MB 45897 (detrifluoromethyl sulfinyl fipronil) | 200 | 1000 | Increased liver weight + microscopic changes | Johnson (1995) |

| COMPOUND | NOEL (mg/kg bw) | LOEL (mg/kg bw) | ENDPOINT | REFERENCE |
|---|---|---|---|---|
| SHORT-TERM REPEAT-DOSE STUDIES (DOG) | | | | |
| Fipronil | 1 | 10 | Neurological signs; increased Hb and RBC | Holmes (1991a) |
| MB 46513 (desulfinyl fipronil) | - | 1 | Clonic convulsions | Dange (1995b) |
| MB 45950 (fipronil sulfide) | 5 | 15 | Increased ALP, Hct, Hb, RBC | Broadmeadow (1991a) |
| SUBCHRONIC STUDIES (RAT) | | | | |
| Fipronil | 0.3 | 2 | Increased liver and thyroid weights | Holmes (1991b) |
| Fipronil (neurotoxicity) | 0.3 | 7.5 | Neurobehavioural changes | Driscoll and Hurley (1993) |
| MB 46513 (desulfinyl fipronil) | 0.03 | 0.2 | Clinical signs | Dange (1994b) |
| MB 45950 (fipronil sulfide) | 0.7 | 1.8 | Increased liver weight; thyroid follicular cell hypertrophy | Broadmeadow (1991b) |
| SUBCHRONIC STUDIES (DOG) | | | | |
| Fipronil | 0.5 | 2 | Neurobehavioural changes | Driscoll and Hurley (1993) |
| MB 46513 (desulfinyl fipronil) | 0.27 | 1 | Clinical signs | Dange (1996) |
| CHRONIC STUDIES (RAT) | | | | |
| Fipronil | 0.02 | 0.06 | Clinical signs of neurotoxicity; increased thyroid weight; decreased T4 levels; increased severity of progressive senile nephropathy | Aughton (1993) |
| MB 46513 (desulfinyl fipronil) | 0.025 | 0.1 | Increased mortality, increased incidence of convulsions | Bigot (1998) |
| DEVELOPMENTAL STUDIES (RAT) | | | | |
| Fipronil | Maternal: 4<br>Foetal: 20 | Maternal: 20<br>Foetal: – | Maternal: decreased bodyweight gain<br>Foetal: no effects at the highest dose tested | Brooker and John (1991) |
| Fipronil (neurotoxicity) | Maternal: 0.9<br>Offspring: 0.05 | Maternal: 8.7<br>Offspring: 0.9 | Maternal: bodyweight loss<br>Offspring: reduced pup weight during lactation | Mandella (1995) |
| MB 46513 (desulfinyl fipronil) | Maternal: 0.2<br>Foetal: 1 | Maternal: 0.5<br>Foetal: - | Maternal: decreased bodyweight gain<br>Foetal: no effects at highest dose tested | King (1990) |

## EFFECTS ON THE LIVER AND THYROID

Following repeated dosing with fipronil, liver weights were increased in mice and rats, with an isolated finding in one animal in the 12-month dietary study in dogs, with no associated pathology. Increased liver weight generally occurred at dose levels exceeding 1 mg/kg bw/day, though a marginal increase was seen in male rats treated at 0.5 mg/kg bw/day fipronil in the diet for 4 weeks (Peters et al. 1990). Microscopic changes to the liver were generally minimal, comprising mainly peri-, centri- or pan-acinar fatty vacuolation and hepatocyte enlargement in rats and mice, with focal necrosis and chronic degenerative changes also in mice. Hepatocytic carcinomas were also reported in mice (Broadmeadow 1993), but their incidence was well within the historical control range, and they were not considered to be relevant to human health. In contrast to fipronil, liver weights were unaffected by desulfinyl fipronil, but there were observations of pale liver, with centrilobular hypertrophy in mice the main microscopic finding (Bigot 1996).

Effects of fipronil on the thyroid were seen in rats, but in the one study that measured T3/T4 levels in dogs, no changes were seen. Thyroid weights were increased in rats, and this was usually associated with thyroid follicular cell hypertrophy and/or hyperplasia at the microscopic level (e.g. Aughton 1993). Plasma levels of T4 were decreased, and TSH was increased, but reductions in T3 levels were inconsistent (Peters et al. 1991). Increased levels of T4-conjugated products were found in the bile, and a study using $^{125}$I-thyroxine demonstrated that treatment with fipronil increased T4 clearance from blood (Peters et al. 1991). Fipronil did not affect iodine organification in the thyroid (Peters 1991a). These findings are consistent with fipronil acting indirectly on the thyroid by increasing the loss of thyroid hormone through the liver. As a result of this increased excretion, modulation of the hypothalamus–pituitary–thyroid axis is expected to occur, leading to a compensatory increase in TSH secretion and consequent stimulation of the thyroid gland, manifested as hypertrophy and possible progression to follicular cell neoplasms[7]. This proposed mechanism of disruption of thyroid homeostasis in rats has been demonstrated for a range of xenobiotic chemicals, and because of the differences between rats and humans with respect to thyroid biochemistry and physiology, the effects on the thyroid in rats are not considered to be relevant to human health risk assessment. In the chronic/carcinogenicity study in rats, an increase in both benign follicular cell adenomas and follicular cell carcinomas of the thyroid was seen, but these neoplastic changes were considered to be related to treatment only at a relatively high level of exposure (13 mg/kg bw/day) in the presence of clear NOELs. Taking into account the lack of relevance of this mechanism of toxicity to humans, these changes are not of concern to human health.

No changes in thyroid weight were detected in the studies with desulfinyl fipronil, and though some changes in T3/T4 levels were reported in the short-term and subchronic rat studies, these were very inconsistent and the assay appeared unreliable. Also in contrast to fipronil, there was no change in TSH levels. Overall, it appears that desulfinyl fipronil does not share the thyroid stimulating effects of the parent compound. With the exception of fipronil detrifluoromethyl sulfone for which thyroid hypertrophy was noted in a single study (28-day dietary study in rats) at a very high dose in a single sex (males, 916 mg/kg bw/day), no thyroid effects were observed for the other metabolites tested, but all had the effect of increasing liver weight.

---

[7] Capen CC, Dybing E, Rice JM and Wilburn JD (Eds) 1999, 'Species differences in thyroid, kidney and urinary bladder carcinogenesis', *IARC Scientific Publications No.147*.

### GENOTOXICITY

Fipronil produced negative results in several genotoxicity tests *in vitro* (Clare 1988a; Lloyd 1990; Marshall 1988a) and one *in vivo* (Edwards 1995), but positive results were obtained in an *in vitro* chromosomal aberration test using Chinese hamster lung cells (Wright 1995). However, a similar study using human lymphocytes with higher concentrations of fipronil was negative for this same genotoxic endpoint. Also taking into account the negative results in the other genotoxicity studies, and the lack of evidence for carcinogenicity being the result of a genotoxic mechanism in chronic rodent studies (as opposed to reactive hyperplasia, i.e. a threshold mechanism), fipronil is not a genotoxic hazard.

Of the fipronil metabolites/degradates tested, there was only one positive finding from 19 studies. This occurred with RPA 097920 (detrifluoromethylsulfinyl fipronil), a rat metabolite of fipronil sulfone, in an *in vitro* chromosomal aberration test using human lymphocytes, and only in the absence of metabolic activation, with a high level of cytotoxicity (Johnson 1995). No other genotoxicity studies were performed on RPA 097920 (detrifluoromethylsulfinyl fipronil), but as no carcinogenicity concerns have arisen from the fipronil rat chronic study in which rats would be expected to be exposed to this metabolite, the positive finding in the genotoxicity study is not of particular concern. The weight-of-evidence indicates that fipronil and its metabolites do not present genotoxic hazards to humans.

### REPRODUCTION AND DEVELOPMENTAL EFFECTS

No developmental abnormalities were reported for fipronil administered to rats and rabbits at oral doses up to 20 mg/kg bw/day and 1 mg/kg bw/day respectively. The reproduction study (King 1992) in rats showed reduced litter size and pup viability in the F0, and a slight reduction in mating performance and fertility index in F1 animals at 27 mg/kg bw/day. In common with the other rat studies, thyroid and liver effects were observed for the parental animals, though a decrease in pituitary weight was also noted (all at 2.5 mg/kg bw/day). Convulsions were recorded for both pups and dams in the reproduction study, but these occurred only at the relatively high dose of 27 mg/kg bw/day. Fipronil does not cause reproductive toxicity at levels of exposure relevant to humans.

## 3.1.3 Establishing health intake values

### ADI

To establish an ADI, a summary of results determined in those studies deemed adequate for regulatory purposes are shown in Table 3 (fipronil) and Table 4 (desulfinyl fipronil) below.

**Table 3: Toxicological results from studies using fipronil**

| SPECIES | STUDY TYPE | NOEL (mg/kg bw/day) | LOEL (mg/kg bw/day) | EFFECT | REFERENCE |
|---|---|---|---|---|---|
| SUBCHRONIC | | | | | |
| Rat | 13 weeks, dietary | 0.3 | 2.0 | Increased liver and thyroid weights | Holmes 1991b |
| Dog | 13 weeks, capsules | 0.5 | 2 | Inappetence and reduced bodyweight gain (females) | Holmes 1991c |

| SPECIES | STUDY TYPE | NOEL (mg/kg bw/day) | LOEL (mg/kg bw/day) | EFFECT | REFERENCE |
|---|---|---|---|---|---|
| CHRONIC | | | | | |
| Mouse | 78 weeks, dietary | 0.05 | 1.2 | Increased liver weight and microscopic changes to the liver | Broadmeadow 1993 |
| Rat | 89-91 weeks, dietary | 0.02 | 0.06 | Clinical signs of neurotoxicity; increased thyroid weight; decreased T4 levels; increased severity of progressive senile nephropathy | Aughton 1993 |
| Dog | 52 weeks, capsules | 0.2 | 2 | Clinical signs of neurotoxicity, bodyweight loss | Holmes 1992 |
| Dog | 52 weeks, dietary | 0.3 | 1 | Clinical signs of neurotoxicity | Holmes 1993 |
| REPRODUCTION | | | | | |
| Rat | 2-generation reproduction, dietary | Parental: 0.25 | Parental: 2.5 | Parental: increased thyroid and liver weights; decreased pituitary weight; increased incidence of follicular epithelial hypertrophy of the thyroid | King 1992 |
| | | Offspring: 2.5 | Offspring: 27 | Offspring: reduced survival; reduced bodyweight gain; developmental delays | |
| Rat | Developmental neurotoxicity, dietary | Maternal: 0.9 | Maternal: 8.7 | Maternal: bodyweight loss | Mandella 1995 |
| | | Offspring: 0.05 | Offspring: 0.9 | Offspring: reduced pup weight during lactation | |
| DEVELOPMENTAL | | | | | |
| Rat | Developmental, gavage | Maternal: 4 | Maternal: 20 | Maternal: decreased bodyweight gain | Brooker and John 1991 |
| | | Foetal: 20 | Foetal: – | Foetal: no effects at the highest dose tested | |
| Rabbit | Developmental, gavage | Maternal: 0.2 | Maternal: 0.5 | Maternal: decreased bodyweight gain | King 1990 |
| | | Foetal: 1 | Foetal: - | Foetal: no effects at highest dose tested | |

**Table 4: Toxicological results from studies using desulfinyl fipronil**

| SPECIES | STUDY TYPE | NOEL (mg/kg bw/day) | LOEL (mg/kg bw/day) | EFFECT | REFERENCE |
|---|---|---|---|---|---|
| Mouse | 90-day, dietary | 0.3 | 1.7 | Deaths | Bigot 1996 |
| Rat | 90-day, dietary | 0.03 | 0.2 | Clinical signs | Dange 1994b |
| Dog | 90-day, dietary | 0.27 | 1.0 | Clinical signs | Dange 1996 |
| Rat | 2-year, dietary | 0.025 | 0.1 | Increased mortality, increased incidence of convulsions | Bigot 1998 |
| Rat | Developmental, gavage | Maternal: 0.2<br>Foetal: 1 | Maternal: 1<br>Foetal: 2.5 | Maternal: reduced bw gain<br>Foetal: retarded skeletal ossification | Foulon 1997 |

The current ADI for fipronil of 0.0002 mg/kg bw/day was set in 1994, based on a NOEL for neurological signs and haematological changes in a chronic dietary study in rats and a 100-fold safety factor to account for intra- and inter- species variation. Examination of the new studies (Holmes 1993; Mandella 1995; see Table 3) indicates that the rat is the species most sensitive to chronic dietary exposure, and hence remains the most suitable species on which to base the ADI upon in the absence of human data. Furthermore, results in the rat are closely supported by a chronic dietary study in mice (Broadmeadow 1993). The NOEL in the chronic rat study (0.02 mg/kg bw/day) is less than the NOELs in the reproduction (0.25 mg/kg bw/day, King 1992) and developmental studies (lowest NOEL 0.05 mg/kg bw/day; Mandella 1995), and therefore is protective of these endpoints.

In repeat-dose studies, the mammalian metabolite, MB 45950 (fipronil sulfide), was of lower toxicity than the parent compound, and so does not need to be considered further here. Limited studies provided for other metabolites indicate that their toxicity is low relative to the parent compound also. As the photodegradate desulfinyl fipronil is not a mammalian metabolite, and is present as a residue in plants, its toxicity must be considered when setting the ADI. The NOELs/LOELs for fipronil and desulfinyl fipronil in their respective chronic dietary studies showed that the two compounds produce toxic effects at similar doses following long-term exposure. Therefore, basing the ADI on the NOEL from the fipronil chronic rat study will also cover potential hazards from chronic dietary exposure to desulfinyl fipronil. The results of the developmental study with desulfinyl fipronil indicate that this will also be protective of developmental effects for the photodegradate. The information available for fipronil sulfone and fipronil sulfide indicates that they have similar toxicity to the parent. Therefore, using a safety factor of 100, and the NOEL from the chronic rat study for fipronil, the ADI is maintained at 0.0002 mg/kg bw/day. This is a group value to cover fipronil, desulfinyl fipronil, fipronil sulfide and fipronil sulfone.

### ARfD

The current ARfD is 0.02 mg/kg bw, based on a combined NOEL of 2.5 mg/kg bw/day from two acute neurotoxicity studies in rats and a safety factor of 100. This value is described in the ARfD list as ‘a group value for fipronil, fipronil-desulfinyl, fipronil-sulfenyl and fipronil-sulfonyl’. This value was incorporated into the ARfD List in 2006. A summary of the studies relevant to the ARfD is provided in Table 5.

**Table 5: Summary of results from toxicological studies for establishing an ARfD**

| SPECIES | STUDY TYPE | NOEL (mg/kg bw/day) | LOEL (mg/kg bw/day) | EFFECT | REFERENCE |
|---|---|---|---|---|---|
| FIPRONIL | | | | | |
| Rat | Acute neurotoxicity | 2.5 | 7.5 | Reduced footsplay | Hughes 1997 |
| Rat | Acute neurotoxicity | 0.5 | 5 | Reduced footsplay | Gill 1993 |
| Rat | Developmental | Maternal: 4<br>Foetal: 20 | Maternal: 20<br>Foetal: – | Maternal: decreased bodyweight gain<br>Foetal: no effects at the highest dose tested | Brooker and John 1991 |
| Rat | Developmental neurotoxicity | Maternal: 0.9<br>Offspring: 0.05 | Maternal: 8.7<br>Offspring: 0.9 | Maternal: bodyweight loss<br>Offspring: reduced pup weight during lactation | Mandella 1995 |
| Rabbit | Developmental | Maternal: 0.2<br>Foetal: 1 | Maternal: 0.5<br>Foetal: – | Maternal: decreased bodyweight gain<br>Foetal: no effects at highest dose tested | King 1990 |
| DESULFINYL FIPRONIL | | | | | |
| Rat | Acute neurotoxicity | 2 | 12 | Reduced footsplay, slow righting reflex, decreased locomotor activity, drop in rectal temperature | Hughes 1996 |
| Rat | Developmental | Maternal: 0.2<br>Foetal: 1 | Maternal: 1<br>Foetal: 2.5 | Maternal: reduced bw gain<br>Foetal: retarded skeletal ossification | Foulon 1997 |

The previous ARfD of 0.003 mg/kg bw, was based on a NOEL of 0.3 mg/kg bw/day for neurobehavioural effects from a three-month neurotoxicity study in rats, and a safety factor of 100. This value was adopted from Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on 10 January 2001. The rationale given by the JMPR for basing the ARfD on a NOEL from a repeat-dose study, was 'because of concern about the prolonged toxicokinetics of fipronil' (JMPR 1997). While it is agreed that fipronil and its metabolites are eliminated slowly, and with repeated dosing there is a likelihood of accumulation, the submitted acute neurotoxicity studies in rats have been given primary consideration in setting the ARfD. The 14-day follow-up period in the acute neurotoxicity studies was considered adequate for the observation of any delayed effects.

More recently, the no-effect level for fipronil of 2.5 mg/kg bw in the acute neurotoxicity study of Hughes (1997) was considered the most appropriate study on which to base the ARfD. A similar earlier study (Gill 1993) resulted in a no-effect level of 0.5 mg/kg bw, but the LOEL in the study of Gill exceeded the NOEL in

the Hughes study. These acute neurotoxicity studies share a similar neurobehavioural endpoint of reduced footsplay. The LOELs for these studies were established at 7 hours post-dosing, judged by the authors as the time to peak effect. In a preliminary acute neurotoxicity study, rats were submitted to FOB testing at 2, 4 and 7 hours following a single oral dose of 25 mg/kg bw. Convulsions were seen in one male at 4 and 7 hours and one female at 7 hours, chewing action in one male at 4 and 7 hours, lip licking in two females at 7 hours, and wet anogenital regions in both sexes at 7 hours. However, no later test points were considered. In another preliminary study, one male (50 mg/kg bw) had convulsions at 5 and 24 hours post-dosing, and another (80 mg/kg bw) at 4–7 hours. In the toxicokinetic studies, $C_{max}$ in the plasma occurred at 4–6 hours after a dose of 4 mg/kg bw. Therefore, as the LOELs in the main studies occurred at doses of 5–7.5 mg/kg bw, it is a reasonable estimate that effects at these doses coincided with $C_{max}$, and therefore represent a true time of peak effect. It is unlikely that effects occurred at doses lower than the LOELs, and were overlooked due to selection of the incorrect time of peak effect.

As the NOELs in the rat developmental neurotoxicity study (Mandella 1995) and the rabbit developmental study (King 1990) are less than 2.5 mg/kg bw/day, the possibility that the effects observed in these studies may have arisen from a single dose needs to be considered here. The endpoint in common to these studies is decreased bodyweight gain. This was also seen in the acute neurotoxicity studies, so a possible acute effect must be considered. In the case of the rat developmental neurotoxicity study, maternal bodyweight loss was observed at about 8.7 mg/kg bw/day (NOEL 0.9 mg/kg bw/day). However, in the rat reproduction study, maternal bodyweight gain was reduced at 27 mg/kg bw/day, but not at 2.5 mg/kg bw/day (King 1992). Therefore, taking dose selection into account, the combined maternal NOEL is 2.5 mg/kg bw/day, equal to the NOEL in the acute neurotoxicity study. Comparison of the developmental neurotoxicity study with the reproduction study is appropriate, as in both of these studies the test material was delivered in the diet, and treatment continued into the lactation period. In the developmental neurotoxicity study, pup weights at birth and during lactation were slightly reduced at about 0.9 mg/kg bw/day (3–9%), with a NOEL of 0.05 mg/kg bw/day. This is in conflict with the results in the rat reproduction study, in which reduced pup weight at birth and pup weight gain until weaning were observed at 27 mg/kg bw/day, but not at 2.5 mg/kg bw/day. This calls into doubt whether the small reduction in pup weight at 0.9 mg/kg bw/day in the developmental neurotoxicity study constitutes a biologically significant effect. Also, taking into account that these changes are unlikely to have arisen from a single dose, this endpoint was not considered an appropriate basis for the ARfD. The maternal LOEL in the rabbit developmental study is 0.5 mg/kg bw/day, again based on reduced bodyweight gain. However, the intragroup variability was high, and reduced bodyweight gain was largely attributable to relatively low food consumption confined to the interval spanning gestation days 13 to 19. As the biological significance of the reduced weight gain is debatable, and there is a strong likelihood that the apparent reduced weight gain in this study was not due to a single treatment, the rabbit developmental study was also not considered an appropriate basis for the ARfD.

As for the ADI, the toxicity of desulfinyl fipronil should also be considered here. The effects in the developmental study were associated with reduced food consumption in the dams during treatment, with consequent reduced bodyweight gain, and delayed ossification in the foetuses is expected to be secondary to maternal toxicity. These effects are unlikely to have arisen from a single dose, so are not relevant to the ARfD. The no-effect level for desulfinyl fipronil in an acute neurotoxicity study (Hughes 1996) was 2 mg/kg bw. The doses used in the fipronil and desulfinyl fipronil studies do not allow a precise comparison of the relative toxicity of the two compounds in the acute neurotoxicity tests. For practical purposes, as similar no-effect levels were demonstrated for the two compounds, with a similar endpoint, it is appropriate to base the ARfD on the NOEL of 2.5 mg/kg bw from the acute neurotoxicity study for fipronil, and incorporating

a safety factor of 100 for inter- and intra-species variability. Toxicity studies indicate that the acute toxicity of fipronil sulfone and fipronil sulfide is similar to that of fipronil. Other metabolites/degradates are less acutely toxic than fipronil, so they do not need to be considered further in this context. The recommended ARfD was therefore 0.02 mg/kg bw, and this is the value included in the current ARfD List. This is a group value to cover fipronil, desulfinyl fipronil, fipronil sulfide and fipronil sulfone.

### 3.1.4 Human exposure

In Australia, fipronil is registered for a range of agricultural uses, including seed dressings, the control of locusts and a wide range of insect pests in bananas, brassicas, cotton, potatoes, sugarcane and in turf. Fipronil is also included in a number of bait products for use by householders and commercial building treatments. Home veterinary products containing fipronil are registered for use on cats and dogs.

#### DIET

Fipronil has not been included in the Australian Diet Surveys (formerly known as Market Basket Surveys). It was detected in 1 out of 293 barley samples in the National Residue Survey (NRS) 2003-04 at 0.046 mg/kg of the whole grain. The traceback investigation was inconclusive and could not confirm the reason for the contravention, as there was no evidence of fipronil use. As fipronil is not registered for use on barley, it was suggested that there might have been contamination from previous fipronil treatments of canola. The NRS 2002-03 reported the detection of fipronil residues in 2 out of 45 samples of canola, but no further details were provided. Other crops that were sampled, but in which no residues of fipronil were found in the NRS from 2002-03 to 2004–05, were sorghum, pecan nut, lupin, wheat (whole grain, bran and flour), oat, field pea and chick pea. Note that this review did not include a consideration of risk from intake of residues in food.

#### WATER

Information is lacking with respect to likely public exposure to fipronil from drinking water. Fipronil is not included in the WHO (2004) guidelines for drinking-water quality under ‘Guideline values for chemicals from agricultural activities that are of health significance in drinking water’ nor is it listed under ‘Chemicals from agricultural activities excluded for guideline derivation’, or ‘Chemicals from agricultural activities for which guideline values have not been established’. The current Australian Drinking Water Guidelines (NHMRC 2004) do not include a guideline value or a health value for fipronil; however, the draft revised Australian Drinking Water Guidelines (2009) propose a guideline health value of 0.0007 mg/L, with a comment that fipronil is unlikely to be found in drinking water at levels that may cause human health concerns. Fipronil is not expected to be present in drinking water at detectable levels, other than as a result of spillage or through misuse. The agricultural use of fipronil may potentially lead to contamination of source waters through processes such as runoff, spray drift or entry into groundwater, however the exposure of the general population is expected to be well below levels that may cause health concerns.

#### NON-DIETARY EXPOSURE CONSIDERATIONS

Products available for home veterinary/home garden (HV/HG) use that are considered in this review include the spray and spot-on products for use in cats and dogs, and insect baits. The risk assessment for the exposure to the insect baits is straightforward, due to the low concentrations of fipronil in these products. The non-dietary exposure to fipronil that may occur during the use of HV products for the treatment of tick

and flea infestations in cats and dogs, or through subsequent contact with a treated pet is considered below. Occupational exposure to fipronil is considered separately in the OHS review.

### *Dermal and inhalation exposure during application of veterinary products*

For the veterinary spray formulation, the most likely route of exposure will be dermal when applying the product, restraining or carrying the wet animal, or other incidental contact. Inhalation exposure is expected to be minimal. The safety directions recommend that users wear rubber gloves. The level of user exposure is not expected to be of toxicological concern and this is supported by the findings of an exposure study of pet groomers.

For the veterinary spot-on products, dermal exposure is unlikely when applying the product, however accidental dermal exposure cannot be ruled out. Exposure by inhalation is not expected, as fipronil is not volatile. Any dermal exposure should be transitory and not of toxicological concern if the safety direction 'wash hands after use' is followed.

### *Exposure from handling a treated pet*

Eight pet-stroking studies were submitted for evaluation to assess the exposure and risk from handling treated pets. Exposure of an adult to more than one treated pet or to a very large dog has been assessed as not being of toxicological concern. Separate risk assessments have been conducted for children, as residues may be dislodged onto clothing as well as exposed areas of the body during their interaction with pets, toddlers may be exposed to toxicants through hand-to-mouth transfer, and children may touch the treated site shortly after application and while it is still wet. The calculated margins of exposure (MOE) were acceptable.

No additional consideration was required for the Frontline spot-on formulations with (S)-methoprene (Frontline Plus), as the addition of (S)-methoprene does not alter the product hazard profile and the products are packaged similarly, with the same method of application as Frontline Top Spot.

## 3.1.5 Skin reactions in humans

The toxicity of fipronil primarily in relation to dermal irritation and the induction of skin sensitisation is of particular interest, as the APVMA has received a number of adverse experience reports that included skin reactions in humans. These reports primarily involved veterinary chemical products.

The laboratory animal toxicity data have been summarised in Section 3.1.1. The weight of evidence from laboratory animal studies of fipronil and its formulated products indicates that fipronil is not a skin sensitiser in guinea pigs.

Information available on the allergenicity of each of the excipients in Frontline Spray, and those common to the Frontline Spot-on range of products has also been considered. No animal skin sensitisation data were located for the alcohols present in these products. Limited human testing was generally of poor quality, but there was some evidence to suggest that human sensitisation to these alcohols may occur in some individuals. However, in the context of their long history of widespread use, such reactions are very rare, and on this basis they are not expected to have contributed to the adverse reactions.

Thus the animal data do not indicate a skin sensitisation potential for fipronil or Frontline products.

Merial provided its Australian and international databases of human adverse experience reports to assist in the APVMA review of fipronil. The OCSEH assessed the adverse experience reports and also sought expert opinion from an expert clinical dermatologist.

## HUMAN ADVERSE EXPERIENCE REPORTS FOR FRONTLINE PRODUCTS IN AUSTRALIA

Up to February 2006, the OCSEH was aware of 73 adverse experiences reports associated with Frontline products, which dated back to 1998. Of these, 30 were due to accidental exposure or related to off-label use, and are not discussed further. Another 12 reports were not pursued due to confounding factors such as underlying chronic illnesses and associated medication, symptoms inconsistent with the toxicology profile of fipronil (taking route of exposure into account), or insufficient information.

Of the remaining cases, the majority (23, or 74%) were cutaneous in nature, with pruritus, rashes, hives, blisters and/or angioedema reported. Other reported symptoms included burning sensation of the eyes/face (3), sore/watery eyes (3), puffy or swollen face, lips, tongue or limbs (8), headache (2), shortness of breath (1) chemical taste (1), persistent shortness of breath (1), and facial numbness (1). There was a single case that reported various symptoms including diarrhoea, lethargy, nausea, cramps, fever and incoordination. The severity of symptoms varied from slight (resolved overnight with no intervention other than washing the affected area) to severe reactions involving hospitalisation (two cases). With a few exceptions, adverse reactions were of sufficient concern to the affected party that a medical practitioner was consulted.

The time and onset of symptoms was generally less than 48 hours after contact with the product or a treated animal, and these symptoms were frequently treated with cortisone and/or antihistamines. In many cases the outcome of this treatment was not provided in the report, though a positive response to treatment was documented for ten cases. Seven individuals reported a recurrence of symptoms that could potentially be associated with exposure to the product or a treated pet.

In several cases, the product had previously been used without incident for an extended period of time, but in other instances (6 out of 31 cases), reactions were reported after using the product for the first time.

Of the 31 individuals reporting cutaneous effects, 13 (42%) had a history of intolerances or allergies to other substances such as food, plants, medicines or other chemicals. That is, 13 individuals had pre-existing conditions influencing their immune response (i.e. atopic). Consequently, these individuals are considered susceptible to allergic contact dermatitis, and care should be taken in using such data to determine the skin sensitisation potential of Frontline products. For the remaining 18 individuals, it cannot be definitively determined from the limited details in the adverse experience reports whether the absence of statements on intolerances or allergies means these individuals are not susceptible to allergic contact dermatitis (i.e. non-atopic).

Descriptions obtained through the Adverse Experience Report Program were assessed by an expert clinical dermatologist. The dermatologist was of the opinion that some of the reports of adverse reactions might be consistent with allergic contact dermatitis, but it is difficult to be sure, and that irritant contact dermatitis is another possible cause of these dermal reactions. The advisor was of the opinion that the Adverse Experience Report Program provided a much needed surveillance for adverse reactions; however, the

information was not of sufficient detail to identify a sensitiser, but was useful in identifying areas of concern which require follow-up and appropriate testing.

It is the nature of adverse experience reports that they lack the detail that could potentially provide a more definitive link between the symptoms experienced and exposure to Frontline products. Consequently, the nature and time of onset of many of the reported symptoms and their recurrence upon repeated exposure in a small number of individuals provides only limited evidence to suggest that Frontline products may be the causative agent.

For observed cutaneous effects, the limited information in adverse experience reports (i.e. a lack of diagnostic patch testing) also means that it cannot be conclusively determined whether the observed skin effects were irritant or allergic in nature. However, it is noted that in skin irritation tests on rabbits, fipronil provided divergent results (i.e. slight skin irritation in one study and no skin irritation in another), while Frontline spot-on was a slight irritant, and Frontline Spray was not a skin irritant. Therefore, the data suggest that direct contact with the spot on product during application, or while still wet on the animal, may produce skin reactions that are irritant in nature. However whether the amount of fipronil on a treated animal's coat would be sufficient to provoke skin irritation in persons coming into contact with the animal is not known.

It should be noted that the reported incidents may represent only a proportion of similar responses in the community, as adverse reactions to agricultural and veterinary chemicals are typically under-reported. On the other hand, it is noteworthy that the number of Australian adverse experience reports for Frontline Top Spot, Frontline Plus, and Frontline Spray for cats and dogs (omitting those due to accidental exposure or off-label use; when confounding factors were present; if they were inconsistent with the toxicological profile of fipronil; or those for which there was insufficient information), peaked in 1999 (8 out of 10 reports clustered in January to March), and has since decreased (summarised in Table 6). The reason for this is not known.

**Table 6: Annual incidence in Australia of reported adverse reactions to Frontline Top Spot, Frontline Plus and Frontline Spray for cats and dogs**

| 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|---|
| 1 | 10 | 4 | 5 | 4 | 3 | 2 | 2 |

## COMPARISON OF HUMAN ADVERSE EXPERIENCE REPORTS FOR FRONTLINE PRODUCTS WORLD-WIDE AND IN AUSTRALIA

To assist in the determination of the skin sensitisation potential of Frontline products, Merial submitted its international database of human adverse experiences with these products for the years 2000 to 2003 inclusive. Of the 1772 suspected human adverse experiences reported for this period worldwide, 76% can be divided into two main categories—cutaneous reactions (815 out of 1772 reports; 46%) and ocular exposure incidents (536/1772; 30%). This distribution was similar for the intervals 2000–2001 and 2002–2003. The Merial Australian database for 2000–2003 showed that cutaneous incidents were high (23 out of 33; 70%) relative to the worldwide incidence shown above, though this difference is unlikely to be significant given the relatively few Australian reports. Compared to the spot-on formulations, there were many fewer adverse experiences associated with Frontline Spray. However, the number of human adverse reactions reported for each formulation type was approximately in proportion to the number of doses sold, both

worldwide and for the Australian subset of results, and this is likely to have influenced the distribution of adverse outcomes.

Data from industry suggest that around 1.92 million households in Australia have used a fipronil containing ectoparasiticide. In Australia, it is this demographic (i.e. the household) from which nearly all human adverse reports for Frontline products arise. Using the maximum number of adverse experience reports of 10 reported in one year (mean of 4), the annual incidence is low at one per 500,000 households. The proportion of doses applied by veterinarians, who are more likely to be wearing protective clothing when using the product and handling a treated animal, is not known; however, it is probably only a very small proportion of the number of doses applied. The European Medicines Agency EMEA (EMEA 2006) refers to human incident data for veterinary products in general, but states that it is unlikely to be established beyond a reasonable doubt that incidents were caused by the products. The report also refers to skin reactions from products containing fipronil and gives a possible explanation for this as increased awareness of the reporting system.

Of the 1772 adverse reports in the *Merial Worldwide Database 2000–2003*, Merial identified 920 as 'Reports with signs even potentially consistent with hypersensitivity occurring after Frontline exposure 2000–2003'. The vast majority of these were cutaneous reactions. Examination of this subset of reports reveals that the presence of a hypersensitivity reaction was unlikely in about half of these cases (e.g. stinging when product entered a laceration, localised tingling and numbness, chemical taste, and various confounders), but in the remainder, representing approximately 25% of reported incidents, it is agreed that the reported reactions (mostly comprising hives, rashes, and pruritus) are possible immune reactions. Approximately one third of these cases represented reactions in individuals who did not apply the product but came into contact with a treated pet. For the latter, at times it was reported that contact was made prior to the product drying on the animal, but in many instances, contact was recorded as having occurred after the product was dry, or at a sufficient length of time after application for this to be assumed. Approximately 10% of reports consistent with allergic reactions stated that the affected person had other allergies, but it is not known if this information was routinely requested.

The French AFSSA/AFSSE report (2005) examined human adverse experiences reported worldwide. The data included cases of exposure to both veterinary and agricultural products. Around 300 cases of adverse experiences following exposure to veterinary products during treatment of an animal or handling a treated pet were provided to the French CAP-TV (a Poison and Toxicant Monitoring Center). Of these, most were the result of accidental ocular exposure, and only 10 reported cutaneous symptoms. Of those exhibiting dermal lesions, three persons were known to have other allergies, and one had concurrent illness considered responsible for the cutaneous lesions. One other person failed to develop lesions following re-exposure to the product. The remaining five people exhibited erythema, non-characterised rash persisting for four days, skin irritation, burning lips, blisters at point of contact, and/or hives and oedema of the eyelids. Aside from one case, which reported the absence of cutaneous lesions following subsequent exposure, there is no information regarding follow up or a definitive diagnosis by an expert clinician.

Overall, the types of scenarios and symptoms described in the overseas adverse reports, and the level of detail provided in the reports, were similar to those seen in Australian reports.

## HUMAN ADVERSE EXPERIENCES WITH OTHER FIPRONIL PRODUCTS

The APVMA's Adverse Experience Reporting Program for Agricultural Chemicals did not commence until the end of 2003, so information from this sector is much less complete than for veterinary products. In 1999, the OCSEH reviewed an incident that occurred the previous year, in which two pilots involved in the aerial sowing of rice treated with fipronil reported stinging lips, irregular taste in mouth, inflamed feeling in throat, watering eyes, sore throat, burning eyes and throat, and stinging on the forehead, cheeks, ears and neck. At the time, these symptoms were considered inconsistent with the toxicity profile of fipronil or the fipronil product used for treatment of rice. The OCSEH is not aware of any similar subsequent events.

In 2005, an incident involving pest control operators applying a fipronil product in a sub-floor space was reported. One worker (apparently wearing the prescribed personal protection equipment) experienced swelling of the face and neck that commenced one hour into a treatment process of approximately 1.5 hours duration, with symptoms subsiding one hour after completion of the job. Another worker reported burning of the skin around the eyes, mouth and cheeks. In these instances, the symptoms were consistent with non-active constituents in the product, so the possible role of fipronil in their aetiology is not clear.

The French AFSSA/AFSSE report (2005) examined human adverse experiences that had been reported worldwide, including exposure to agricultural products. In the French CAP-TV (Association des Centres Antipoison et de Toxicovigilance) data consisting of 417 acute cases, only five professionals are reported to have developed dermal symptoms (pruritus), with limited additional information provided. Agricultural products were also represented in the domestic situation, with four cases reported of dermal symptoms evident in persons occupying treated premises. The symptoms reported include 'skin eruptions', hives and a burning sensation. However, in all nine cases, the CAP-TV rated fipronil as being 'doubtful' for being responsible for the reported effects. Likewise, other international databases assessed in this French report, including data from the United States and the United Kingdom, indicate exposure to fipronil-containing products is largely associated with 'benign lesions', such as irritation to the eye and skin following topical exposure.

The AFSSA/AFSSE report included a summary from a study assessing neurobehavioural effects in 76 workers in production plants in the United States and Indonesia. This showed blood serum levels of 6-308 ng/mL for fipronil and its primary metabolite. Although this is indicative that workers are in fact being exposed to fipronil, despite (the assumed) use of personal protective equipment, the actual route of exposure and presence or absence of dermal lesions is unknown from the summary provided. None of these employees showed signs of neurotoxicity on clinical examination or during the psychometric tests to which they were submitted.

Documentation was provided to the OCSEH from occupational physicians in a fipronil manufacturing plant in France (124 employees) and formulating plant in Brazil (53 employees). This documentation states there have been no cases of skin irritation or sensitisation since operations began in 1997 in France and 2005 in Brazil, as noted in routine medical surveillance.

Overall, despite the widespread use of fipronil in agricultural products used in large volumes and varied use patterns, there are only limited reports of cutaneous adverse effects. From the current Australian and International monitoring databases, there is no robust evidence that fipronil causes skin sensitisation.

## FIPRONIL METABOLITES

The possibility that the reported sensitisation reactions could be attributable to metabolites of fipronil present on the coats of treated animals should also be considered. Studies that quantified the levels of fipronil that could be dislodged by stroking treated animals showed that fipronil metabolite levels (fipronil sulfone and fipronil sulfide) in these samples were very low, and frequently below the limit of detection. Also, photodegradates of fipronil are formed on exposure to sunlight. The primary photodegradate, desulfinyl fipronil, was found to be associated with the coats of treated dogs that had been allowed access to sunlight for around 6 hours/day for 2 weeks, with levels of the photodegradate reaching up to 6% of fipronil present (Astruc 1998). No information was available regarding the sensitisation potential of fipronil metabolites.

## SUMMARY AND CONCLUSIONS

- The results of 12 skin irritation studies in rabbits, two of which were on the active constituent, indicate fipronil is a slight skin irritant.
- The results of 12 skin sensitisation studies in guinea pigs, two of which were on the active constituent (Buehler and Magnusson and Kligman method), indicate that fipronil and its products were not skin sensitisers in guinea pigs.
- Though sales figures do not provide an accurate representation of the number of households that use these products and, thus, the number of people potentially exposed, the number of human adverse reports to Frontline products is relatively low compared to sales figures.
- The Australian adverse experience reports provide limited information with little or no follow-up information. Taken individually, each individual adverse report does not provide a definitive causative link to the product. When considered together, the evidence is only suggestive that the observed adverse effects may be due to exposure to Frontline products. The international data are similarly limited.
- For the observed cutaneous effects in the adverse experience reports, it cannot be reliably determined from the limited information whether they were irritant or allergic in nature. No human patch tests for allergenicity to fipronil appear to have been performed. Similarly, although some reports indicated that cutaneous effects were seen in some individuals using the product for the first time (i.e. would be irritant in nature), given the potential widespread use of Frontline products prior exposure through contact with treated pets or their environs cannot be ruled out (i.e. reported skin reactions may be allergic in nature).
- Although it is not known if an individual's history to allergies was routinely requested, approximately 10% and 40% of worldwide and Australian adverse reports respectively were seen in individuals who were susceptible to allergic contact dermatitis. Care should be taken in using such data to determine the skin sensitisation potential of Frontline products, as skin reactions seen in such individuals may not be reflective of what would be observed in the general population.
- An irritation and sensitisation study on the primary photodegradate, desulfinyl fipronil, would provide additional data on the irritant and skin sensitisation potential of this photodegradate, which may be of some assistance in interpreting the cutaneous reactions described in adverse experience reports.

Thus, the animal data provide no robust evidence of a skin sensitisation potential for fipronil or Frontline products. In humans, although cutaneous effects have been seen in adverse experience reports their incidence is relatively low compared to sales figures, the information contained in such reports do not provide a causative link to Frontline products, and the nature of the skin reactions (irritant or allergic) cannot

be reliably determined. Furthermore, although it cannot be established if an individual's history to allergies was routinely determined, skin reactions were often seen in individuals with pre-existing conditions influencing their immune response (40% of individuals reporting an adverse cutaneous effect in Australia). Thus, the available practical experience in humans does not reliably demonstrate Frontline products to be capable of inducing a skin sensitisation reaction in a substantial number of people.

Therefore, both the available animal and human data provide no reliable evidence that fipronil or Frontline products are skin sensitisers, however fipronil is associated with slight skin irritation.

### 3.1.6 Consideration of first aid instructions and safety directions

#### FIRST AID INSTRUCTIONS

The OCSEH recommends that first aid instruction 'a' remains appropriate for products containing fipronil, except for products containing both fipronil and thiodicarb. For products containing both fipronil and thiodicarb, first aid instructions 'a' and 'h' should be replaced by first aid instruction 'm'. (See Section 4.3.1 for details of the recommended first aid instructions).

#### SAFETY DIRECTIONS

Toxicology studies were provided for many of the products or for formulations that are sufficiently similar to Australian registered products that they may be used in establishing the acute toxicity of those products (see Section 3.1.1 for a summary of the acute toxicity studies). Where no product toxicity data were available, the acute toxicity profiles were estimated from the characteristics of the individual constituents and their respective concentrations in each product.

The OCSEH has recommended revisions to the hazard-based label safety directions for a number of currently registered products and has also recommended hazard-based statements applicable to other products that are not covered by a FAISD Handbook entry. As the OCSEH review of the available animal and human data concluded that the data provide no reliable evidence that fipronil or Frontline products are skin sensitisers, safety statement '180' (Repeated exposure may cause allergic reactions), where currently included, is to be deleted from the relevant fipronil products. Other changes to the safety directions are also recommended for some products. The OCSEH also recommends that the warning statement currently on the veterinary products concerning hypersensitivity to insecticides or alcohol (''Do not use [PRODUCT NAME] if you or your pet have a known hypersensitivity to insecticides or alcohol'') be removed, as it is considered misleading. Table 7 summarises the outcomes of the toxicology assessment of the safety directions for fipronil products:

**Table 7: Outcomes of the toxicology assessment of the safety directions**

| OUTCOME | SAFETY DIRECTION |
|---|---|
| No change | HG BA 0.5 g/kg or less in plastic labyrinth |
| | BA 3.4 g/kg or less in propylene glycol impregnated in cardboard * † |
| | GR 1 g/kg or less |
| | WG 800 g/L or less |
| | UL 25 g/L or less |
| New entry | BA gel 0.5 g/kg or less |
| Amended entry | HV SA 100 g/L or less |
| | HV LD 2.5 g/L or less |
| | SC 500 g/L or less, more than 200 g/L |
| | SC 200 g/L or less, more than 100 g/L |
| | SC 100 g/L or less |
| | DU 5 g/kg or less with bentonite PD all strengths * †† |
| | Thiodicarb SC 400 g/L or less with fipronil 80 g/L or less |
| Deleted entry # | EC 300 g/L or less |
| | WP 10 g/kg or less |
| | HG WP 10 g/kg or less |
| | GB 0.2 g/kg or less |
| | HG BA gel 0.5 g/kg or less |

** These entries have only been evaluated in terms of sensitisation and the necessity for the 180 statement. The remaining safety directions were not reviewed in either the toxicology or OHS reports as the entry occurred after the data-call in period for the Fipronil Review.*

*† This entry is expressed as 'BA 0.03 g/station or less in propylene glycol impregnated in cardboard' in the toxicology and OHS reports in Volume 2.*

*†† This entry is expressed as 'DU 5 g/kg or less' in the toxicology and OHS reports in Volume 2.*

*# The current entries for fipronil EC 300 g/L or less, WP 10 g/kg or less, HG WP 10 g/kg or less and GB 0.2 g/kg or less should be deleted as there are no registered products in these categories. The current entry for HG BA gel 0.5 g/kg or less should be deleted, as it is included under the new entry BA gel 0.5 g/kg or less.*

The recommended safety directions from the separate toxicology and OHS assessments have been combined and are listed in Section 4.3.2.

## 3.2 Occupational health and safety (OHS)

The OHS assessment for the review of fipronil was undertaken by the Office of Chemical Safety and Environmental Health (OCSEH). The OCSEH considered all the OHS data and information submitted for the review. The OHS findings are summarised below. The complete report is in Volume 2.

Fipronil belongs to the phenylpyrazole family and acts by blocking the GABA-regulated chloride channels. It is a broad-spectrum insecticide and is used to control insect pests in a wide range of agricultural crops. Fipronil products are also used as insecticidal seed dressings and for the control of termites, cockroaches and ants in residential and commercial buildings. In veterinary situations, fipronil products are used as spray-on or concentrated spot-on formulations to control fleas and ticks on cats and dogs.

A risk assessment of fipronil products intended for commercial application indicated that safety directions on product labels needed to be revised. In particular, chemical resistant clothing; chemical resistant footwear and gloves are required when mixing/loading SC formulations by open mixing/loading systems. Workers applying the diluted product by hand application method (including for termite treatment) will also need respiratory protection in addition to the above personal protective equipment. For all other application methods, one layer of clothing, with or without gloves, is considered to provide adequate protection. Risk to farmers treating peatmoss (mushroom cultivation) or treating seed (except by commercial treaters) could not be quantified due to lack of appropriate exposure data or exposure models. Exposure to fipronil is likely to occur when applying diluted product during these treatment methods. Workers would therefore need to wear cotton overalls or equivalent clothing and gloves.

Safe re-entry intervals were calculated for each crop, taking into account the amount of fipronil applied and the degradation of fipronil on foliage. The photolytic metabolite of fipronil, fipronil-desulfinyl (MB 46513), has repeat-dose toxicity similar to that of the parent compound, resulting in the same end point for both compounds. A default 1% degradation rate for fipronil or its metabolite was assumed for risk assessment and re-entry interval calculations. Considering the type and duration of the post-application activities, a NOEL from a short-term dermal study was used. Results indicated a zero-day re-entry interval (i.e. when the spray has dried) for all applications except brassica and turf. Exposure estimation during post-application activities in brassica (hand harvesting, irrigation, pruning, topping, tying mature plants) indicated an unacceptable risk to workers in the absence of personal protective equipment for up to 13 days after application. A re-entry interval of 13 days for hand harvesting, irrigation, pruning, topping, tying mature plants is recommended, unless wearing cotton overalls or equivalent clothing and chemical resistant gloves. Exposure estimation during post-application activities in turf (hand-weeding and transplanting) indicated an unacceptable risk to workers in the absence of personal protective equipment for up to 35 days after application. A re-entry interval of 35 days for hand-weeding and transplanting turf is recommended, unless wearing cotton overalls or equivalent clothing and chemical resistant gloves.

The air concentration of fipronil in dwellings treated for termite control was found to be very low and considered unlikely to pose an unacceptable risk to residents occupying the areas soon after treatment.

All veterinary uses were assessed qualitatively. The following re-handling statement is recommended for fipronil animal spray product labels: ‘Animals treated with fipronil spray formulations should not be handled till the spray has dried. If prior handling is required, workers should wear rubber gloves’.

### 3.2.1 Use patterns of fipronil products

The uses of fipronil, as described on product labels, are outlined in Table 8.

## Table 8: Use patterns of fipronil products

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| Bananas | Banana rust thrips | Butt application:<br>200 SC: 150 mL/100 L water (0.03%)(0.75 mL/stool)<br>800 WG: 37.5 g/100 L water (0.03%)(0.19 g/stool)<br>Band application:<br>200 SC: 40 mL/100 $m^2$(or 4 L product in 1300 L water/ha; 0.062%)<br>800 WG: 10 g/100 $m^2$(or 1 kg product in 1300 L water/ha; 0.062%) | One application two months prior to bunch emergence. | Butt application: Applied as a coarse spray covering the stem to a height of 30 cm and the soil in a 30 cm radius from the stem base. A total volume of 500 mL solution is applied per stool (Hand spraying either as knapsack or handgun connected to spray tank).<br>In Australia, the Cavendish variety is grown at a density of 1800 plants per hectare and the Lady's Finger variety is grown at a density of 800 plants per hectare (Information provided by NSW DPI).<br>Band application: Applied as a 30 cm wide band on each side of the butt. Applied with a side delivery boom and nozzles are adjusted to spray at least 30 cm of soil on either side of the butt and to a height of 30 cm up the stem.<br>Applied at a minimum water volume of 13 L/100 $m^2$ (trash removed) or 26 L/100 $m^2$ (trash retained). |
| | Banana weevil borer | | | Apply by butt application as described for banana rust thrip.<br>Applications should be made in Spring and/or Autumn when weevil numbers reach or exceed acceptable threshold levels.<br>This use is subject to an Avcare Resistance Management Strategy |
| Brassicas (head cabbage, cauliflower, broccoli, Brussels | Diamondback moth, cabbage white butterfly, cabbage cluster | 200 SC: 250 mL/ha (0.005-0.0125%)<br>800 WG: 60 g/ha (0.0048-0.012%) | No more than four applications per year, preferably applied within an 8-week | Spray volume of between 400 and 1000 L/ha according to crop size are recommended.<br>Aerial application not recommended. |

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| sprouts, kohlrabi | caterpillar | | period. | This use is subject to an Avcare Resistance Management Strategy. |
| Grapevines | Fig longicorn | 200 SC: 100 mL/100 L (0.02%)<br>800 WG: 3.1 g/100 L (0.0025%) | Apply as a single spray | Apply only as a high volume directed spray using hand-held equipment (500 mL per vine). Thorough coverage of vine trunks and cordons is essential for effective control (Suggested spray volume – 800 L/ha).[8] |
| Cotton | Cotton thrips<br>Green mirid | 200 SC: 62.5 – 125 mL/ha (0.07% maximum in ground spray and 0.125% maximum in aerial spray)<br>800 WG: 15.5 – 30 g/ha (0.07% maximum in ground spray and 0.12% maximum in aerial spray) | Number of applications not specified on the labels[9] | Spray volume of 35 – 75 L/ha for ground spraying and 20 – 50 L/ha for aerial spraying (according to the size of the plants).<br>Apply at first sign of pest. Use higher rates in situations of high thrips pressure.<br>For the control of Green mirid, apply spray to achieve thorough coverage of foliage when pest first appears and repeat as required. Use the higher rate under sustained heavy Green mirid pressure. The product is compatible with early season IPM, with the lower rate having less impact on beneficials |

[8] Spray volume used by the registrant for risk assessment conducted.

[9] Number of applications on these crops is not specified on product labels. The OCSEH received advice from Nufarm Australia that a maximum of two applications per year are made in these crops.

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| Potatoes | Wireworm<br>Mole cricket | 200 SC: 250 mL/ha (0.018-0.025%)<br>800 WG: 62.5 g/ha (0.018-0.025%) | Once before planting potatoes | Apply as a broadcast spray to the surface of the soil and incorporate to a depth of 15 cm prior to planting.<br>200-280 L spray/hectare (Information provided by the registrant at the time of registration of this use pattern).<br>Aerial application not recommended |
| | White fringed weevil | 200 SC: 500 mL/ha (0.036-0.05%)<br>800 WG: 125 g/ha (0.036-0.05%) | | |
| Pasture, Sorghum | Australian Plague locust, Spur throated locust, Migratory locust, Wingless grasshopper | 200 SC: 6.25 mL/ha (0.0025% in ground spray and 0.00625% in aerial spray)<br>800 WG: 1.5 g/ha (0.0024% in ground spray and 0.006% in aerial spray) | Number of applications not specified on the labels[10] | Apply diluted with water to a minimum of 20 L/ha by air or 50 L/ha by ground rig, directly onto locusts.<br>Ensure thorough coverage of foliage.<br>Where inaccessibility prevents direct spraying of locusts apply as a barrier treatment (minimum 25 m wide) ahead of advancing hopper bands. |
| | Plague locust, Spur throated locust, Migratory | 3 UL: 420 mL/ha (1.26 g ai/ha) | | Apply undiluted by aircraft through ULV spray units as a spray directly onto locusts. |

[10] Number of applications on these crops is not specified on product labels. The OCSEH received advice from Nufarm Australia that a maximum of two applications per year are made in these crops.

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| | locust | 8.5 UL: 150 mL/ha (1.28 g ai/ha) | | Apply by aircraft through ULV spray units undiluted or diluted with compatible spraying oil. |
| Turf, lawns and golf courses | Arg. Stem weevil, Funnel ant, Mole cricket | GR: 30 – 75 kg/ha (30-75 g ai/ha) | Number of applications not specified on the labels[9] | Distribute granules evenly on turf surface at the first signs of pest activity. Ensure incorporation with at least 6 mm of rainfall or overhead irrigation immediately after application. |
| Sugarcane | Sugarcane weevil borer | 200 SC: 2 to 5.7 mL/100 m row (0.01 – 0.03%)<br>800 WG: 0.5 to 1.4 g/100 m row (0.01 – 0.03%) | Number of applications not specified on the labels[11] | Apply in a minimum water volume of 250 L/ha (approx. 3.8 L/100 m row). Use the higher rate when pest pressure is heavy. Apply during summer months when the crop has produced the first millable internode of cane. Use hollow cone nozzles as a directed spray to cover the base of the sugarcane stools and up to the stalk to a height of 40 cm. Treat both sides of the stool ensuring coverage of all stalks, soil and trash in an area to 10 cm either side of the stools. |
| | Sugarcane | Single row plantings: | | |

[11] Number of applications on these crops is not specified on product labels. The OCSEH received advice from Nufarm Australia that a maximum of two applications per year are made in these crops.

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| | wireworm | 200 SC: 1.1 mL/100 m single row length<br>800 WG: 0.3 g/100 m single row length<br>Double row plantings:<br>200 SC: 1.8 mL/100m double row length<br>800 WG: 0.5 g/100 m double row length | | Apply in the planting furrow over the top of the plant pieces (setts), in sufficient water to ensure coverage of the plant pieces and the surrounding soil.<br>Total volume of water per double row length or per hectare not provided. Hence final concentration of fipronil in the spray solution could not be calculated. |
| Mushrooms | Mushroom flies | 100 SC: 32 mL/300 L bale of peatmoss (0.064%)<br>200 SC: 16 mL/300 L bale of peatmoss (0.064%)<br>800 WG: 4 g/300 L bale of peatmoss (0.064%) | Apply mixture once during preparation of peatmoss<br>(Once per crop, but several cycles of mushroom production per year). | Prepare solution by mixing the products with a small volume of water (5 L).[10,12]<br>Apply mixture to peatmoss during preparation of casing. Ensure thorough mixing with peatmoss. |
| SEED TREATMENT | | | | |
| Canola | Red-legged earth mite | 500 SC: 400 mL/100 kg seed (20%) for high volume spray | Where greater pest numbers are anticipated or where there are more than 8 | Ensure thorough coverage of seed. Add 400 mL product to 600 mL of water per 100 kg seed. |

[12] Information obtained from mushroom growers.

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| | | | mites per plant, alternative or additional treatments will be required | |
| Sorghum, Sunflower | False wireworm<br>Black field earwig | 500 SC: 150 mL/100 kg seed (15%) | - | Thoroughly coat seed using commercial seed coating equipment. Add 150 mL of product to 350 mL of water/100 kg seed. |
| Rice | Bloodworm | 500 SC: 20 mL/100 kg seed or 25 mL/ha | - | Use on seed through BASF approved equipment. |
| Cotton | False wireworm<br>Cotton thrips | 80 SC (with 400 g/L thiodicarb): 625 mL/100 kg seed (5%) | - | Thoroughly coat seed using commercial seed coating equipment. Allow to dry before handling. |
| BAITS | | | | |
| Domestic, commercial and public service areas | Cockroach infestations | Gel 0.5 g/kg: 0.03–0.06 g spot size. (0.03 mg fipronil max). Apply 1-3 spots per $m^2$. | Reapply according to remaining level of infestation, when bait is no longer visibly present. | For heavy infestations, the number of spots is increased to 3 per $m^2$. |

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| TERMITE TREATMENT | | | | |
| Chemical soil barriers around existing buildings and structures | Subterranean termites | 100 SC:<br>Vertical barriers:<br>600 mL in 70 - 100 L water (0.06 – 0.086%)<br>Horizontal barriers:<br>600 mL in 60–100 L water (0.06 – 0.1%) | As with all chemical termiticides, regular inspections (at least annually) is recommended as bridging and breaching of barriers can occur.<br>The need for re-treatment should be determined as a result of these inspections. | Spray equipment should be calibrated to deliver a low-pressure high volume coarse spray. Apply to form a continuous chemical soil barrier (horizontal and vertical or as an external perimeter) around and under the structure to be protected as per AS3660.2.<br>The barrier may be created using a combination of conventional spraying and trenching. Application of chemical barriers beneath the concrete slabs and paths will require drilling and injection of termiticide using rodding equipment. Rodding is to be used only where trenching and treating the backfill is not possible. Chemical barriers that have been disturbed will need to be re-applied to restore the complete barrier.<br>Spray volume<br>100 L/$m^3$ for vertical barrier<br>5 L/$m^2$ of soil surface for horizontal barrier<br>Note: In heavy soil, lower spray volumes may be used to prevent run-offs. In such cases, however, the concentration of ai should be increased in the spray solution so that the same amount of active is applied per given area or volume of soil (eg 0.086% ai if only 70 L/$m^3$ solution is used in vertical barrier and 0.1% ai if only 3 L/$m^2$ is used for horizontal barrier). |
| Protection of poles and fence posts | | 600 mL in 100 L water(0.06%) | | Only poles and posts in contact with soil need to be treated. For existing posts and poles, create a continuous barrier 450 mm deep and 150 mm wide around the post or pole trenching and puddle treating the backfill. Soil injection equipment must only be used where trenching or back-filling is not possible or rodding, or trench and puddle treat back-fill. Use 100 L of prepared spray per cubic meter of soil around the pole or post.<br>If new poles are being installed then the bottom of the hole and the back-fill should be treated at installation. |

| CROP / SITUATION | PEST | PRODUCT: APPLICATION RATE / DILUTION (MAX. CONCENTRATION OF ACTIVE INGREDIENT (ai) IN SPRAY) | FREQUENCY OF APPLICATION | COMMENTS / LABEL INSTRUCTIONS |
|---|---|---|---|---|
| Dogs and cats | Fleas, flea allergy dermatitis, ticks and biting lice on dogs and cats and sarcoptic mites on dogs | 2.5 LD (for spray treatment) (0.25% fipronil) | Applied fortnightly or monthly depending on the pest to be controlled | Spray treatment—product is packaged in spray bottles. Each trigger pump releases 0.5 mL product (1.5 mL from 250 and 500 mL bottles). A maximum of 6 mL/kg bw of the animal, equal to 12 trigger pumps/kg, (or four trigger pumps from 250 and 500 mL bottles) is sprayed. For example, for a 12-kg animal, 144 trigger pumps (or 48 trigger pumps from 250 and 500 mL bottles) delivering 72mL of product (7.5–15 mg fipronil/kg) are applied. |
| | Fleas, flea allergy dermatitis, ticks, biting lice and sarcoptic mites in dogs | 100 SA (with or without 90 g/L methoprene), for spot treatment (10% fipronil +/- 9% methoprene) | | Spot-on treatment—product containing 100 g fipronil/L is packaged in 0.5 mL pipettes for use on cats and in 0.67, 1.34, 2.68 or 4.02 mL pipettes for use on dogs (depending on the bodyweight of dogs). The tip of the pipette is broken and the entire amount is applied on the skin of the animal. For dogs, the dosage varies with the bodyweight of the animal and a minimum of 6.7 mg fipronil/kg bw of animal is applied.<br><br>The Startgard range comprises kits of one tablet from the Heartgard range (active constituents ivermectin, or ivermectin and pyrantel) and one pipette from the Frontline Top Spot or Frontline Plus range. As these kits are intended for the treatment of puppies and kittens, the pipettes are the smallest sizes in the Frontline ranges (0.5 mL for kittens and 0.67 mL for puppies). |
| | Fleas, flea allergy dermatitis and biting lice in cats | 100 SA (with or without 120 g/L methoprene), for spot treatment(10% fipronil +/- 12% methoprene | | |

### 3.2.2 Methods and types of equipment used for mixing/loading/application of fipronil products

Fipronil products are used for their insecticidal actions in agricultural as well as non-agricultural situations. In the agricultural situations, fipronil products are used in broadacre crops, bananas, grapevines, mushrooms and on turf. In non-agricultural situations, they are used for termite, ants and cockroach control and as insecticidal seed dressing.

Fipronil products are also used in veterinary situations as spray-on or concentrated spot-on formulations for the control of ectoparasites on cats and dogs.

#### BROADACRE CROPS, BANANAS, GRAPEVINES AND TURF

In broadacre crops, fipronil products are applied by ground or aerial application. Ground application is mostly by boom sprayers, although hand-held application is also used in some crops. Banana plants and grapevines are treated by hand-held application. Products are diluted with water according to label instructions and loaded in the spraying equipment. Workers mixing/loading for ground spraying (boomspray or hand-held) normally use the open-pour method.

Granular formulations of fipronil are used on turf. No dilution is required. The granules are evenly spread by mechanical spreaders. The label directs users to ensure that incorporation by rainfall or irrigation occurs.

ULV formulations are applied by aerial spraying for locust control. The product is used either undiluted or diluted with compatible spraying oil. The diluted or undiluted product is directly loaded into the aircraft or spray tanks from bulk containers by mechanical means.

#### INCORPORATION INTO MUSHROOM CASING

Mushrooms are grown on compost, which is pasteurised and placed in large trays or beds. Mushroom spawn is worked into the compost and the growing takes place in specially constructed houses, where the farmers can regulate the crucial aspects of heat and humidity.

In two to three weeks, the compost becomes filled with the root structure of the mushroom, a network of lacy white filaments called mycelium. At that point, a layer of pasteurized peat moss (casing) is spread over the compost. The peat moss is treated with fipronil products just prior to layering over the compost. The process of mixing diluted product with peatmoss is usually mechanised; applied by spray boom fixed to the top of peat moss turning machine. The casing is applied evenly as a 4–5 cm thick layer over the compost. The quantity of product handled at any time will depend on the extent of the mushroom beds to be treated. Hand-held space spray, though used sometimes, is the least preferred method of application as spawn run rooms and growing rooms are kept closed to personnel as much as possible to prevent cross-contamination. In commercial enterprises, approximately 50 batches of mushrooms are grown per year, with new casing prepared for each batch.

#### TREATING SEED

In Australia, seeds are mostly treated by professional seed treaters in completely enclosed systems. Bulk containers of fipronil product are connected via an inlet pipe to the application equipment. The mechanical

treaters measure the required amount of product and dilute it with water to the required volume. Seed to be treated is loaded into a hopper for treatment within the machine. Dry treated seed emerges from the machine through a funnel into sacks, which are sealed either mechanically or by hand.

At some seed-treating facilities, grain is treated as a coarse shielded spray (20% fipronil) as it comes on a conveyor belt for storage. A small minority of farmers may treat their own seed in an open system—generally as batch treatment in a cement mixer type arrangement or a semi-closed system (closed except for the final transfer to bins or bags).

#### TERMITE CONTROL

For termite control, fipronil product is applied by hand-held equipment including low-pressure hand wand and soil injection (rodding). The low-pressure hand wands used for applying termiticides are different from those used for foliar spray in that the hand wand for termiticide application delivers a high-volume, coarse 'jet', which is more like pouring the solution rather than spraying. The procedure is to dig a trench and pour in the diluted product with a watering nozzle on the end of a rod that is approximately 0.5–0.75 m long. This floods the soil below ground level and there is less likelihood of spray drift.

#### BAIT TREATMENT

A bait formulation of fipronil is used to control cockroaches in domestic, commercial and public service buildings. The product, available in 35 g tube, is applied as tiny spots (1–3 spots per $m^2$) in the infested area.

#### APPLICATION OF VETERINARY PRODUCTS TO CATS AND DOGS

Veterinary products for use on dogs and cats are either spray-on treatment or spot treatment. Although the products are meant for use by the general public (pet owners), commercial pet groomers may also use the products to treat dogs and cats. Both types of formulations (spray and spot-ons) are ready-to-use products and do not require diluting or mixing before use.

Label instructions for the Frontline Spray ready-to-use product require the user to spray the entire animal against the lay of the hair, using a pump nozzle applicator held 10–20 cm from the animal's coat. The coat is to be ruffled as the spray is applied, so the product penetrates down to the skin, and the coat is thoroughly wet. Occasionally workers may rub the product into the animal's skin and, to avoid spraying into the dog's eyes, nose, and mouth, workers spray one or more pumps into their hands and then rub the dog's face to cover the face.

The method of application of the Frontline spot-on range of products involves breaking the snap-off top from the pipette, then while holding the pipette tip against the skin of the animal, squeezing the pipette several times until it is emptied of its contents. Frontline Top Spot is applied monthly for the control of fleas and flea allergy dermatitis in dogs and cats, and brown dog ticks and mange in dogs. It is applied fortnightly for the control of paralysis ticks in dogs. Lice treatment is as directed.

### 3.2.3 Toxicological hazard of fipronil

The toxicological hazard of fipronil has been summarised in Section 3.1.

### 3.2.4 Toxicological endpoints for OHS risk assessment

Considering the mode of action of fipronil, namely inhibition of the GABA-gated chloride channels in neurons, it seems appropriate that the endpoint most relevant for an OHS risk assessment will be associated with its pharmacological action, which in the case of fipronil, is a neurotoxicity effect.

Fipronil products intended for professional use will be applied by farmers, spray contractors and pest control operators. The most likely route of exposure for farm workers and pest control operators would be by dermal contact with the undiluted products, spray mixture and treated vegetation (re-entry workers). Inhalation of fipronil in spray aerosols may also occur. Dermal and inhalation studies are therefore appropriate for selection of NOELs for risk assessment.

Agricultural workers are likely to be exposed on a seasonal basis, as dictated by pest pressure and the growth cycle of plants under production, whereas pest control operators may be exposed to the chemical throughout the year. Dermal and inhalation NOELs must therefore be set for assessment of occupational risk using data generated over timescales appropriate to the likely frequency and duration of exposure. It is therefore considered appropriate to use a NOEL from a short-term study for estimation of risk to farmers (or contract sprayers) and a NOEL from a chronic study to estimate occupational risk to pest control operators.

A review of the existing toxicological database revealed that repeat dose inhalation studies for fipronil are not available. In the absence of a suitable inhalation study, the NOEL from an oral dose study was used in the assessment of risk from inhalation exposure.

#### SHORT-TERM NOEL (FOR ASSESSING RISK TO FARMERS AND CONTRACT WORKERS)

Fipronil products are generally applied twice per year per crop with a maximum of four applications in brassicas. Contract workers may use the products more often as they would apply these products in several farms. Farmers treat seeds with fipronil products once or twice per season at harvest time only. Commercial seed treaters use fipronil products intermittently and for only short durations during the year.[13] Based on the use pattern, a dermal NOEL of 5 mg/kg bw/day established in a 21-day dermal study in rabbits (Hermansky and Wagner 1993) is considered appropriate for occupational health and safety risk assessment of these workers.

Inhalational exposure to fipronil in an agricultural setting would mostly arise from inhalation of spray mist or dust generated from the granular product. The pattern and frequency of exposure would be the same as for dermal exposure. As user exposure to fipronil products is expected to be intermittent and of short duration, the NOEL of 1 mg/kg bw/day from a 4-week oral study in dogs (Holmes 1991a) will be used for the occupational risk assessment.

[13] Large quantities of rice, sorghum and sunflower seed are treated commercially with fipronil products for 2–3 months per year. However, seed treatment at these large-scale facilities are fully automated and enclosed (Information obtained from Pacific Seeds, Queensland).

#### LONG-TERM NOEL (FOR ASSESSING RISK TO PEST CONTROL OPERATORS)

Pest control operators are likely to be exposed to fipronil products for a major proportion of year and throughout their working life. Based on the use pattern of Termidor, a NOEL from a long-term study in experimental animals was considered appropriate for risk assessment. The 89–91 week oral study in rats yielded a NOEL of 0.02 mg/kg bw/day, with neurological signs at the next higher dose level of 0.06 mg/kg bw/day (Aughton 1993). This NOEL was considered to be appropriate for the OHS risk assessment of pest control operators. Route-to-route extrapolations usually involve a consideration of the internal dose. In the case of oral-to-dermal extrapolation this consideration takes into account of the extent of absorption across the gastrointestinal tract following oral administration. Absorption of fipronil across the gastrointestinal tract was estimated to be 80–90% of the administered dose, taking its biliary excretion into account. Therefore, no correction to the NOEL used for OHS risk assessment is required. (The calculations take into account the extent of dermal absorption). Since a long-term inhalation study is not available, this NOEL will also be used to assess risk from inhalation exposure.

#### NOEL FOR RE-ENTRY INTERVAL CALCULATIONS

Workers may re-enter treated crops after the spray has dried for post-application activities, such as harvesting, pruning or to tend to crops. These 're-entry' workers may be exposed to residues from fipronil and its photodegradation product, which are deposited on foliage or fruit. Exposure would mostly occur by skin contact. Workers are likely to work for a total of 2–3 weeks performing post-application activities. Hence, the dermal NOEL chosen from the short-term repeat dose study to estimate occupational risk for mixer/loaders and applicators (5 mg/kg bw/day) is considered appropriate for establishment of safe re-entry intervals for various crops and post-application activities. The use of the fipronil dermal NOEL is considered to be appropriate for performing the risk assessment for the photodegradation product because there is sufficient evidence to indicate that desulfinyl fipronil is equitoxic to fipronil (see Section 3.1).

### 3.2.5 Assessment of occupational exposure during production

Technical grade fipronil is manufactured overseas. Most of the fipronil products are formulated in Australia from the imported active ingredient. A description of the manufacturing/packaging process, the number of workers involved and personal protective equipment used during formulation and packaging is not available. When involved in the manufacture of veterinary products, workers are expected to adhere to good manufacturing practice (GMP). Adequate quality control, exposure monitoring and risk control measures are under the jurisdiction of the states and territories.

Formulators, laboratory staff and packers handle the active constituent and/or the products and can be exposed to fipronil during the process of formulation and packaging. Individual premises, manufacturing/formulation processes, and exposure control measures may vary within workplaces. Transport workers, storemen retailers and warehouse workers could be exposed to the products if packaging is breached and spillage occurs.

### 3.2.6 Assessment of occupational exposure and risk assessment when handling fipronil products

The registrants provided a number of worker exposure studies and assessments in response to the data call-in by the APVMA. These included:

- a worker exposure study of application of a granular fipronil formulation used in a banana plantation in Cameroon
- a study investigating inhalation exposure to house occupants and pest control operators during and after application of a granular fipronil termiticide formulation in the United States
- a worker exposure study of dermal and inhalational exposure of commercial pet groomers during application of Frontline Spray
- a worker exposure study of dermal exposure of commercial pet groomers during application of Frontline Top Spot
- an operator and post-application exposure and risk assessment for a SC fipronil termiticide formulation in Australia
- a worker risk assessment for a granular fipronil formulation used in corn, potato, rice and cotton in the United States
- an occupational and residential exposure and risk assessment for a granular fipronil termiticide formulation conducted by the United States Environmental Protection Agency (US EPA)
- an exposure and risk assessment for a flowable concentrate seed treatment used in Europe
- a pet groomer exposure analysis and risk assessment for Frontline Spray and Top Spot.

#### ESTIMATION OF OCCUPATIONAL EXPOSURE AND RISK

Very limited chemical specific exposure data are available for fipronil. Some registrants estimated worker exposure using surrogate data. However, these estimates did not cover all use patterns, and in some cases, the parameters used in the estimations did not correspond to an Australian use pattern (for example, number of hectares treated per day by boomspray). The OCSEH has therefore estimated occupational exposure to fipronil using surrogate exposure data from the Pesticide Handlers Exposure Database (PHED, US EPA 1999).

##### *Agricultural use*

Fipronil is registered for agricultural use in a number of different formulations with varying concentrations of the active ingredient. The chemical is used as a foliar spray on outdoor crops and is applied by using boomspray, hand-held equipment or aircraft. The SC products are applied at various dilutions in water ranging from a relatively concentrated 400 mL/L for seed treatment (500 g/L fipronil product), to a very dilute 6.25 mL/50 L for spraying on pasture and sorghum. The ULV products (3 g/L and 8.5 g/L fipronil) are applied by aircraft either undiluted (420 mL/ha and 150 mL/ha, respectively) or diluted (8.5 g/L fipronil product only) to 3.0 L with a compatible spraying oil.

The main route of occupational exposure to fipronil is expected to be by skin contamination during mixing/loading and spraying. Fipronil has very low vapour pressure ($3.7 \times 10^{-9}$ hectoPascals at $25^{o}$C). Inhalation exposure to fipronil during mixing/loading is therefore not expected. Inhalation of spray mist may occur during ground spray application (boomspray or hand-held equipment).

Dermal or inhalation exposure of flaggers to fipronil spray is possible during aerial spraying. There are no chemical specific studies on exposure of flaggers or bystanders. Neither are there any appropriate exposure models to estimate exposure during flagging. It is therefore not possible to estimate risk to these workers.

Occupational exposure for the following nine agricultural scenarios was assessed using the Pesticide Handlers Exposure Database (PHED, US EPA 1999).

### *Scenario (1): Open mixing and loading of SC formulations*

SC formulations, containing 80–500 g/L fipronil, are applied as dilute sprays to crops or in the case of termite control, around domestic and commercial structures. Two of the products, Cosmos Insecticidal Seed Treatment and Semevin Super Seed Dressing Insecticide are used in dilute form for seed treatment. The quantity of fipronil active that is handled per day varies with the application method.

### *Scenario (2): Closed mixing and loading of SC formulations*

Regent products (200 SC and 800 WG) are also applied by aerial spraying to cotton crops and pasture and sorghum. Large volumes of spray are prepared for aerial application, since this method of application can cover about 200 ha/day. Normally, the mixing/loading for aerial application is an automated and closed system.

### *Scenario (3): Mixing and loading of WG formulation*

There is only one product, Regent 800 WG Insecticide (800 g/kg fipronil), with the wettable granule formulation. It is used for the control of a wide range of insect pests in a variety of crops, including mushrooms and is applied as dilute sprays by ground as well as aerial spraying. Repeat applications of the product are indicated for some crops. The quantities of fipronil active handled per day vary with the application method.

### *Scenario (4): Application of diluted products by boomspray*

Fipronil products are applied by boomspray for the control of a range of insect pests in brassicas, potatoes, pastures, sugar cane and cotton.

### *Scenario (5) Application of diluted products by hand-held equipment (knapsack/tank)*

Regent 200 SC and Regent 800 WG are applied by hand-held equipment for the control of a range of insect pests in bananas, mushroom and grapevine. The highest application rate is indicated for bananas.

### *Scenario (6) Application by aircraft*

ULV products (Adonis 3 and 8.5 UL) are applied by aerial spraying either undiluted at the rate of 420 mL and 150 mL respectively (1.275 g fipronil/ha) or diluted (8.5 g/L fipronil product only) to 3.0 L with a compatible spraying oil (APLC, 2004). Regent 200 SC and 800 WG are also applied by aerial spraying on pastures, sorghum and cotton crops. For aerial spraying, Regent products are diluted to give a final concentration of 0.125 % fipronil (maximum).

Human flaggers may be used during aerial application. However, there are no exposure studies or exposure models to estimate exposure during this task.

### *Scenario (7) Application of granular formulation*

Fipronil in granular formulation is applied to turf and lawns for the control of Argentine stem weevil, funnel ants, and mole crickets. Application of granules is normally made using mechanical spreaders. The granules are watered in immediately after application. The application rate is 30–75 g fipronil per hectare.

### *Scenario (8) Incorporation into mushroom casing*

Fipronil products are applied to peatmoss just prior to layering it over the compost in which mushrooms are growing. (This process is called ‘casing’.) The process of mixing diluted product with peatmoss is usually mechanised and applied by a spray boom fixed to the top of peat moss turning machine. Hand held spray, though used sometimes, is the least preferred method of application.

Information on the amount of fipronil used per day for treating peatmoss is not available. The quantity of product handled at any time will depend on the extent of the mushroom beds to be treated. However, mixing/loading and spray application methods are covered under scenarios 1 and 4.

### *Scenario (9) Application of diluted SC formulation for termite control*

The Termidor label recommends the use of a combination of conventional spraying and trenching for termite control. Soil injection (rodding) is recommended only when trenching and backfill is not possible. Hand spraying (to puddle treat backfill for chemical barriers) is therefore considered as the main use pattern for termite treatment.

## DETERMINATION OF OCCUPATIONAL EXPOSURE

PHED was used to estimate dermal and inhalation exposure for workers using fipronil products for scenarios 1 to 9 described above. Spray volumes for hand-held spraying have been modified according to the use patterns of fipronil products (crop spraying and termite control). Hand-held applications (knapsack or motorised hand held sprayer) are carried out for treatment of banana plants. There are no appropriate PHED scenarios or other exposure model to estimate exposure during seed treatment or placing of baits.

The same toxicity endpoint (i.e. neurotoxicity) is applicable to both inhalation and dermal risk assessments; and because dermal and inhalation exposures may occur simultaneously, risks from the two routes were combined to obtain a total risk estimate for occupational exposure.

## OCCUPATIONAL RISK CHARACTERISATION

### *Dermal and inhalation margins of exposure (MOE)*

Potential daily exposure is calculated using the following formula:

Daily Exp. (mg ai/day) = Unit Exp. (mg ai/kg ai) x Max. Appl. Rate (kg ai/ha) x Max. Area Treated (ha/day)

The daily dose is calculated using the following formula:

Daily Dose (mg ai/kg bw/day) = Daily Exp. (mg ai/day)/bodyweight (kg)

Risk to pest control operators was estimated using a long-term NOEL from a dietary study. When NOELs from oral studies are used to estimate risk, a dermal absorption factor is applied to account for the internal (systemic) dose. A 1% dermal absorption for fipronil, derived from comparative *in vitro* dermal studies with human, rat and rabbit epidermis (Walters and Brain 1990; Ward RJ 1997a,b,c) and an *in vivo* rat study (Cheng 1995) (see Section 3.1) was used for risk assessment.

The MOE is calculated using the following formula:

MOE = NOEL (mg/kg bw/day)/Daily dose (mg/kg bw/day)

### *Combined dermal and inhalation MOEs*

Considering that the NOEL used in the risk assessment was established in laboratory animals, a MOE of 100 or more is normally considered acceptable. This MOE takes into account inter- (10x) and intra-species (10x) variability.

### *Evaluation of worker risk estimates*

Mixer/loaders (Scenarios 1–3)

Exposure to fipronil was estimated for workers mixing/loading the product for ground (boom and hand-held spraying) and aerial application and for non-agricultural uses such as termiticide treatment and seed dressing. The amount of product handled per day for the different application methods varies depending on the number of hectares treated by that particular method or the amount of grain treated per day. The MOEs calculated using exposure estimates from PHED indicated unacceptable risks to workers mixing/loading SC formulations for boomspray application, seed treatment (manual treatment) and termite treatment. Although chemical resistant gloves reduced exposures considerably, MOEs were still unacceptable. Chemical resistant clothing is expected to provide 95% protection against contamination (Thongsinthusak et al. 1993). When exposures for mixer/loader wearing chemical resistant clothing were calculated, MOEs were acceptable.

MOEs were acceptable for mixing/loading SC formulations for hand-held application when workers wore just gloves and one layer of clothing. Similarly, for closed mixing/loading, MOEs higher than 100 were obtained only for workers wearing chemical resistant gloves. However, exposure data for workers not wearing gloves were unreliable due to lack of any hand-exposure data.

In the case of seed treatment, where large quantities of product are required to be mixed per day, risk estimates indicated that workers need to wear gloves and chemical resistant clothing even when using closed mixing/loading system.

For mixing/loading dry flowable formulation, exposure was low even when gloves were not worn.

The granule formulation of fipronil is applied to turf for insect control. Mixing of the product is not required; however, the product needs to be loaded in the granule spreader. PHED estimates indicated that risk during loading was low even when workers did not wear gloves.

Applicators (Scenarios 4–7)

Exposure to fipronil when applying the diluted product by boomspray application method was low and did not pose undue risk to workers irrespective of the type of cab used during application, i.e. open or closed cab.

Hand-held application, either with low or high-pressure hand wand, resulted in unacceptable MOEs. MOEs were low even with gloves on. Gloves, chemical resistant clothing (95% protection) and a half-face respirator (90% protection) worn during low-pressure application resulted in a total MOE of 86, which was just below the acceptable margin of safety (100). The same PHED scenario based on mixer/loader/applicator estimates is also applicable to this particular assessment. Use of gloves, chemical resistant clothing and half face respirator in this scenario (low pressure), lowered the risks to within acceptable levels (total MOE = 185). Taken together, and considering the conservative margin of safety (MOE = 100), the risks to users when using low pressure hand-held application equipment are within acceptable levels provided that gloves, chemical resistant clothing and half face respirator are worn during application. Chemical resistant clothing (95% protection) and gloves worn during high-pressure hand-held application resulted in an acceptable margin of safety (MOE = 132).

Fipronil products are also applied aerially either in diluted form or undiluted. PHED estimates for spray application in a fixed winged, enclosed cockpit craft indicated acceptable risk to applicators. Application of granules with the spreader also did not pose any risk to workers even without any PPE, as indicated by the high MOE values.

Mixer/loader/applicators (Scenarios 1–7)

Risk to workers performing both activities—i.e. mixing/loading as well as application—was high for boomspray application method when open mixing/loading and open cabs were used. Risk to these workers was acceptable when they wore gloves or used closed cabs.

For hand-held application, exposures and therefore risk for the combined tasks were high for low-pressure as well as high-pressure applications. Use of chemical resistant clothing (for high-pressure) and chemical resistant clothing and half-face respirator (low pressure), lowered the risks to within acceptable levels.

Risk to workers performing closed mixing/loading and aerial application was high without gloves as indicated by the low MOEs (MOE = 7 without gloves). Use of gloves lowered the risks to within acceptable levels (MOE = 617). Loading and application of granule formulation to turf was considered safe based on the exposure values.

Flaggers

The OHS risk for flaggers cannot be quantified from any surrogate exposure data. Therefore, human flaggers should be protected by engineering controls such as enclosed cabs.

### *Other application methods for fipronil products*

Incorporation of fipronil products into mushroom casing (Scenario 8)

No measured exposure data were available for this use of fipronil. A suitable study does not exist within PHED to estimate operator exposure for this use. A qualitative risk assessment was carried out for this use-pattern. Splashing and spray drift could occur when applying the diluted product to peat moss while it is being turned in the turning machine. Considering the method of mushroom cultivation, preparation of large volumes of spray may not be required. One layer of clothing and chemical resistant gloves should therefore be able to provide adequate protection during mixing/loading of fipronil products. Similar personal protective equipment should be sufficient during application of diluted products by the fixed spray boom. However, if the spray is applied by hand equipment, chemical resistant clothing and a half-face respirator should be worn as indicated by PHED estimation for hand-held low pressure application. Also, since the product is an eye irritant, workers are also required to wear face shield or goggles to prevent eye contamination from any spills or splashes.

Application of diluted SC formulation for termite control (Scenario 9)

A single product, Termidor Residual Termiticide, is under consideration in this review for termite control. Chemical barriers (horizontal and vertical) are installed by pest control operators in Australia using a combination of conventional spraying and trenching. Fipronil is applied by hand-held equipment including low-pressure hand wand and soil injection (rodding). Soil injection (rodding) is recommended only when trenching and backfill is not possible. Hand spraying (to puddle treat backfill for chemical barriers) is therefore considered as the main use pattern for termite treatment.

The low-pressure hand wands used for applying termiticides are different from those used for foliar spray in that the hand wand for termiticide application delivers high volume, coarse ‘jet’, which is more like pouring the solution rather than spraying. The procedure is to dig a trench and pour in the diluted product with a watering nozzle on the end of a rod approximately 0.5–0.75 m long. This floods the soil below ground level and there is less likelihood of spray drift. There are no specific exposure data in the PHED for this particular type of application. The closest is the ‘garden hose end sprayer’ scenario; however, the PHED Exposure Guide (PHED 1998) states that the data for this scenario are of extremely low confidence and should be treated as a data gap. Therefore, this scenario was not considered further. Low-pressure hand-held spray application scenarios in PHED indicate very low dermal and inhalation MOEs without personal protective equipment. Dermal MOEs reached acceptable limits (MOE ≥ 100) with personal protective equipment (gloves and chemical resistant clothing), but inhalation MOEs did not. However, as discussed above, this application technique does not represent the actual trenching method and was therefore not considered further.

Due to a limited amount of method-specific exposure information, the PHED ‘liquid/open pour/termiticide injection’ scenario was considered the most appropriate. This scenario contains exposure data for mixing/loading and application under slab foundation (rodding) and crawl spaces. A limitation is that it does

not have exposures for the trenching method, which is more commonly used to create chemical soil barriers (horizontal, vertical or external perimeter) around or under the structure of existing buildings. Dermal MOE estimates indicate the need for chemical resistant clothing when applying fipronil products by the injection/rodding technique. Using the same scenario, inhalation MOE estimates indicated an acceptable level of risk to workers without respiratory protection. However, a worker inhalation exposure study indicates that the exposure is unacceptable (MOE = 4) during crawl space termiticide injection. A product containing 80 g/kg fipronil was applied in the study, using a variety of spray probes and injectors resulting in a mean worker inhalation dose of 0.0091 mg/kg ai/kg bw (Honeycutt and Kennedy 2001). Considering that Australian pest control operators handle an average of 0.6 kg fipronil per working day, inhalation exposure was estimated to be 0.026 mg/kg bw/day. When applying a NOEL of 0.02 mg/kg bw/day from a chronic oral study, an inhalation MOE of 77 results (0.02 ÷ 0.026 x 100), indicating the need for respiratory protection when applying the termiticide. Based on study results, the exposure may be further reduced with the use of a half-facepiece respirator with combined dust and gas cartridge, which affords 90% protection. The resultant MOE (770) indicates that there is no unacceptable risk (MOE > 100) to the worker provided that a pest control operator uses a half-facepiece respirator with combined dust and gas cartridge when applying termiticides.

Both PHED and worker study estimates are for injectors used in crawl space houses. However, the worker study indicated exposure by inhalation to be some 100 times greater than PHED estimate. Considering this difference in exposure, it is possible that the use of spray probes may contribute to high inhalation exposure compared to injection. Given that the vapour pressure of fipronil is very low ($3.7 \times 10^{-9}$ hPa), the method of application in Australia is more like pouring than spraying (a low pressure, high volume coarse spray), and the surrogate PHED scenario indicated a higher MOE, inhalation exposure is expected to be much lower than that measured in the worker study. However, on the conservative basis that worker study data for spray probe and injector application do indicate a requirement for respiratory protection, the use of a half-facepiece respirator with combined dust and gas cartridge has been recommended during spray preparation and application.

### *Application of diluted product for seed treatment*

Bulk treatment of seed is largely by mechanical process, wherein fipronil product containers are connected via an inlet pipe to the application equipment. The mechanical treaters measure the required amount of product and dilute it with water to the required volume. Seed to be treated is loaded into a hopper for treatment within the machine. Dry treated seed emerges from the machine through a funnel into sacks, which are sealed either mechanically or by hand.

Under normal operating conditions, workers are not likely to come in contact with the spray, unless attaching hoses from the tank to the sprayers or when checking any nozzle blockages. Estimation of exposure during these tasks is not possible. As the seed treatment products are skin irritants, workers will need to wear cotton overalls buttoned to the neck and wrist and elbow-length PVC gloves when carrying out these tasks.

A small minority of farmers may treat their own seed in an open system—generally as batch treatment in a cement mixer type arrangement or a semi-closed systems (closed except for the final transfer to bins or bags). Exposure to fipronil is possible when loading the prepared slurry and when bagging treated seed. There is no appropriate model to estimate exposure during these processes. As the seed treatment products are skin irritants, farmers will need to wear cotton overalls buttoned to the neck and wrist, elbow-length PVC

gloves and a disposable mask when preparing the slurry, using the prepared slurry and bagging treated seeds.

Application of ULV products

Ultra low volume (ULV) products are generally applied undiluted by aerial application. In some instances, the products may be diluted with small volumes of water or oil; however this is achieved by closed mixing/loading. Exposure is therefore expected to be minimal; only when connecting transfer hoses to the product containers. A qualitative risk assessment indicates that chemical resistant gloves are expected to provide adequate protection during this process.

Application of fipronil products as baits

A gel formulation of fipronil is used by professional pest control operators to control cockroaches in domestic, commercial or public service areas. The product, available in 35 g tubes, is applied as tiny spots (1–3 spots per $m^2$) by lightly squeezing the tube or depressing the plunger to dispense the product. An appropriate model/scenario that can be used to estimate exposure for this use pattern is not available. However, because of the tiny amount of the product applied and the method of application, exposure to workers using this product is expected to be minimal.

### *Veterinary use*

Veterinary products for use on dogs and cats are either spray-on treatment or spot treatment. The products are mainly used by pet owners once or twice a month. However, veterinarians and pet groomers may also use the products more frequently. For spray-on treatment, workers normally hold the dog or cat with one hand and operate the spray pump with the other. Occasionally workers also rub the product into the animal's skin and spray one or more pumps into a hand and then rub the dog's face to cover the face to avoid spraying into the dog's eyes, nose, and mouth. The most likely route of user exposure is dermal, although inhalation exposure is also possible. Taking into account that fipronil is present in the product at a low concentration (0.25%); and the vapour pressure of fipronil is low, the level of user exposure is not expected to be of toxicological concern.

With the spot-on treatment, workers hold the animal with one arm while opening the pipette with the other hand and insert the pipette tip through the animal's hair coat near the neck area in order to dispense the contents onto the skin. This procedure is unlikely to lead to the user being dermally exposed to the product, but given the unpredictable behaviour of pets, accidental exposure cannot be ruled out. If the safety direction 'wash hands after use' is followed, any exposure should be transitory and not of toxicological concern. As fipronil is not volatile, exposure by inhalation is not expected.

Studies provided by the registrant indicated low exposure to fipronil residues when dogs were treated with fipronil products as directed by the product label (Meo et al. 1997a,b). Pet groomers or veterinarians may use the product throughout the year. Using a chronic NOEL (0.02 mg/kg bw/day) and a 1% dermal factor, MOEs of approximately 83 and 1280 were calculated from the exposure data for Frontline Spray and Frontline Top Spot, respectively. Although the MOE for Frontline Spray is slightly below the acceptable mark (MOE = 100), consideration should be given to the fact that volunteers in the study treated eight dogs in each session. It is unlikely that pet groomers will treat eight dogs every day all year round).

Workers in both the studies were wearing disposable latex gloves. Although, exposure data 'without gloves' are not available, it can be calculated (assuming that gloves provide 90% reduction in hand exposure) that exposure to fipronil when using Frontline Top Spot is acceptable even when gloves are not worn. Workers using Frontline Spray will however need to wear gloves when treating the animals.

The addition of (S)-methoprene to the Frontline Top Spot formulation does not alter the product hazard profile, so no additional consideration is required for exposure to the Frontline Plus product range. These products are packaged similarly and have the same method of application as for Frontline Top Spot.

## 3.2.7 Assessment of post-application exposure

### AGRICULTURAL USES

Exposure to fipronil residues may also occur when workers enter crops treated with fipronil products for irrigation, weeding, pruning, thinning or harvesting. The type of activity, timing and frequency of re-entry activities is dependent on crop type. Potential worker exposure is determined by factors such as the amount of chemical applied, interval between spraying and re-entry, nature and duration of the particular re-entry activity, density of foliage and spacing of crops and environmental factors that affect the breakdown of residues. Exposure can also occur while sampling treated grain.

Measured exposure data for post-application workers or dislodgeable foliar residue data for fipronil are not available. Exposure to workers entering crops treated with fipronil products was estimated using the default values included in the *US EPA Occupational Post-Application Risk Assessment Calculator Version 1 (8/9/00)-US EPA Policy 003.1*.

#### *Exposure assessment of re-entry workers*

In agricultural situations, fipronil is used in field/row crops (cotton), root vegetables (potatoes), brassica, bananas, grapevines, sugarcane, sorghum, mushrooms, pasture and turf. As mentioned earlier, workers engaged in post-treatment activities such as irrigation, scouting, thinning and harvesting and sampling treated grains may be exposed to fipronil and its degradates, most likely from dermal contact with the treated foliage. Safe re-entry intervals for post-application activities can be determined if dislodgeable foliar residue (DFR) for the chemical and transfer coefficient (TC) for post-application activities are known. These parameters can be used to estimate the dermal exposure using the following formula:

$$\text{Dermal exposure (mg/kg bw/day)} = \frac{\text{DFR (mg/cm}^2\text{) x TC (cm}^2\text{/hr) x T (hr) /BW (kg)}}{1000}$$

The transfer coefficient (TC) is a 'residue transfer index' and indicates the amount of DFR that can be transferred to workers as a function of 'field work activity'. An appropriate TC is used in order to estimate worker exposure from DFR.

#### *Estimation of dermal exposure and safe re-entry periods*

In the absence of actual exposure data, assumptions were used to estimate worker exposure during post-application activities.

Workers entering treated crops for post-application activities may be exposed to fipronil residues and its photodegradation products deposited on foliage or fruit. Workers are likely to work for a total of 2–3 weeks performing post-application activities, and exposure would mostly be by skin contact. Hence, the dermal NOEL chosen from the short-term repeat dose study to estimate occupational risk for mixer/loaders and applicators (5 mg/kg bw/day) is considered appropriate for establishment of safe re-entry intervals for various crops and post-application activities. There is sufficient evidence to indicate that the major metabolite of fipronil, desulfinyl fipronil, is equitoxic to fipronil (see Section 3.1). Consequently, a separate assessment of risk from the photodegradation product was not considered necessary.

### *Calculated risk from occupational post-application exposure*

The results indicated that MOEs for most of the activities were acceptable (MOE ≥ 100) on Day 0 (day of application). It should be noted however that these calculations assume workers enter the field only after the spray has dried. Since no TC values for mushrooms were available, a qualitative risk for workers entering mushroom growing areas was conducted. The re-entry intervals for various crops and agricultural activities derived from the calculations are:

| | |
|---|---|
| Bananas | 0 day (hand-harvesting, stripping, irrigation, weeding mature plants) |
| Brassicas | 0 day (irrigation, scouting, thinning, weeding immature plants)<br>0 day (scouting mature plants)<br>13 days (hand harvesting, irrigation, pruning, topping, tying mature plants) |
| Cotton | 0 day (irrigation and scouting mature plants, hand-harvesting, pruning, skating) |
| Grapevines | 0 day (scouting, training, irrigation) (see text below for re-entry interval for girdling activity) |
| Mushrooms | (see text below) |
| Potato | 0 day (hand-harvesting) |
| Sorghum | 0 day (irrigation, weeding mature/full foliage plants) |
| Sugarcane | 0 day (scouting mature plants) |
| Turf | 0 day (mowing)<br>35 days (hand weeding, transplanting) |

It is noted that, with the exception of brassica crops, all re-entry periods are shorter than their respective withholding periods stipulated on the product labels.

<u>Brassica</u>

The re-entry risk calculation for brassicas was performed assuming the maximum concentration of fipronil applied as a worst-case scenario (50 g ai/ha for Regent 200 SC). Using this approach, the risk to re-entry workers was determined to be minimal from ‘day 0’, for low (MOE = 219) and medium (MOE = 109) exposure activities (irrigation, scouting, thinning, weeding immature plants, scouting mature plants).

However, for high exposure activities (hand harvesting, irrigation, pruning, topping, tying mature plants) the risk to re-entry workers did not reach an acceptable limit until 13 days post-application (MOE = 100).

The following re-entry statements have been established:

> 'Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use. Do not perform high exposure activities including hand-harvesting, irrigation, pruning, topping and/or tying mature plants in brassica for 13 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.'

The withholding period for brassicas on associated product labels (Regent 200 SC and Regent 800 WG) is 7 days for harvest. In the absence of specific information, the re-entry risk assessment has assumed that Australian workers are engaged in high exposure activities for 8 hours a day when handling treated brassicas. A reduction in the handling duration will allow for a shorter re-entry interval. If only a 6-hour duration per day is assumed for workers involved in high exposure activities (hand harvesting, irrigation, pruning, topping, tying mature plants) post-application, the risk becomes minimal from 'day 0' (MOE ≥ 100).

Grapevines

In grapevines, the product will be applied to dormant vines following pruning and prior to budburst; crop management activities are therefore likely to be minimal during this period, except for weeding and irrigation. The risk to re-entry workers was determined to be low from 'day 0', for irrigation and scouting activities. For girdling, the risk was unacceptable even 30 days after application. It should however be noted that the risk calculator assumes foliar contact with workers, consequently if the product is applied to pruned, dormant vines (without leaves), exposure is likely to be low even for girdling activities. Moreover, girdling is done at bloom time or within two or three weeks of ripening which is significantly more than thirty days after spraying.

Mushrooms

Normally, re-entry into mushroom houses is expected to be limited to harvesting operations only. Although mushrooms are harvested manually, picking is usually conducted a few weeks after treatment (normally during spawning) and workers wear gloves to protect the produce (*Australian Mushroom Growers Response to Review of Fipronil*). Since fipronil is applied at the time of preparation of peatmoss (a few weeks before harvesting) and since there is then no mushroom tissue on which fipronil residues could be deposited, under normal use situations, there should be minimal dermal or inhalation exposure during mushroom harvesting.

Turf

The risk to re-entry workers was determined to be low from 'day 0' (MOE = 2333) for the low exposure activity of mowing. When undertaking high exposure activities (handweeding and transplanting), the risk to workers when re-entering treated turf areas was unacceptable (MOE < 100) from 'day 0' (MOE = 74). An acceptable risk for workers undertaking high exposure activities was not achieved until 35 days post-application. The risk assessment assumed a worst-case scenario where workers were involved in high exposure activities for 8 hours per day on a daily basis. The following re-entry statements are recommended:

> ‘Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use. Do not perform high exposure activities including handweeding and transplanting for 35 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day’s use.’

Re-handling treated seed

Treated seed is rehandled by farmers in the cropping process. Seed is transferred from bags or bulk containers to sowing (planting) equipment. Inhalational exposure is possible from the product dust coming off the dried seed. There are no data to estimate inhalation exposure during this process. However, since fipronil has moderate inhalation toxicity, workers should wear a dust mask when handling treated seed.

Re-entering termiticide treated areas

As described in the Honeycutt and Kennedy (2001) study, anyone entering areas/buildings treated with a fipronil-based termiticide is likely to be exposed to fipronil vapour. Dermal exposure is unlikely in the habitable areas of the building because the site of application is usually in areas that are not frequented (i.e. under the concrete slab through drill holes or in the under-house crawl spaces). While it is unlikely that a pest control operator will be required to re-enter the crawl space under a treated house for at least a year, the building occupants and other occupational groups (such as plumbers and electricians) who may use the crawl space are likely to be exposed to some fipronil vapours. For the latter group, some inhalation exposure is likely during drying of the product. The occupational risk assessment for applicators suggests that a re-entry statement advising of this unacceptable risk should be included on the product label. The following statement is considered appropriate for re-entering crawl space areas following termiticide treatment:

> ‘Do not enter treated areas until the spray has dried.’

For the residents of a treated dwelling, the study by Honeycutt and Kennedy showed that the ambient air concentrations of fipronil following Termidor 80 WG treatment was very low, ranging from 0.004 to 0.08 $\mu g/m^3$ and present only on the day of application (Honeycutt and Kennedy 2001). At this air concentration (0.00008 $mg/m^3$), the amount of fipronil inhaled per day will lead to an estimated systemic exposure of 0.00005 mg/kg bw, assuming 100% absorption from the lungs. The acute reference dose established for fipronil is 0.02 mg/kg bw (see Section 3.1.3). Therefore, this exposure is unlikely to have any adverse effect on the residents occupying treated houses even immediately after treatment. Dermal exposure to fipronil after the spray has dried is likely to be minimal.

## VETERINARY SITUATIONS

Exposure to fipronil residues may occur when handling animals soon after product application. Although veterinary ‘spot-on’ products containing fipronil may cause skin irritation, gloves are not required during application due to the limited dermal exposure afforded by the packaging. Likewise, due to the small area treated on the animal, gloves are not required for rehandling.

Veterinary spray products are applied by thoroughly wetting the animal’s coat and hence the exposure to persons applying the product and handling treated animals is much greater. Therefore, when applying the

product, gloves should be worn and treated animals should not be handled until the spray has dried. If prior handling is required, workers should wear rubber gloves.

### 3.2.8 Discussion

In Australia, products containing fipronil are used to control insect pests in a wide range of agricultural and non-agricultural situations (e.g. termite control) and as insecticidal seed dressing in rice, canola, sorghum and cotton. Fipronil is also used in veterinary chemical products as a spray-on or concentrated spot-on formulation to control ectoparasites on cats and dogs.

There is very limited information on occupational exposure to fipronil during mixing/loading and applying fipronil products in a wide variety of crops. A single study measured worker exposure during application of a granular formulation to banana plantation (Pontal 1996). Another study looked at inhalation exposure for pest control operators treating houses with fipronil termiticide (Honeycutt and Kennedy 2001). Exposure assessments, using surrogate data, have been submitted; however, they cover very few use patterns of fipronil products. The OCSEH has therefore used PHED to estimate exposure for most uses of fipronil in order to quantify the risk to workers using fipronil products. Where appropriate surrogate data or exposure models were not available, a qualitative estimation of the risk was conducted taking into account the use pattern and the toxicity hazard profile of the product.

The activities that resulted in an unacceptable risk (MOE < 100) to workers were mixing/loading SC products for boomspray application, grain treatment (open mixing/loading for treating smaller quantities of seed) and termite treatment, even when wearing gloves. The use of chemical resistant clothing, which is reported to provide up to 95% protection (Thongsinthusak et al. 1993), was considered acceptable to sufficiently mitigate exposure during open mixing/loading of SC formulations of fipronil. A single layer of clothing and chemical resistant gloves provided adequate protection to workers mixing/loading SC formulations for hand-held application (smaller volumes as compared to boomspray application) and dry flowable formulations for all methods of application. Workers mixing/loading dry flowable formulations did not need extra clothing or gloves.

Exposure to fipronil was within acceptable levels (low risk) for workers applying the diluted products by boomspray (open or closed cabs) and aerially. For hand-held application, however, exposure was very high with low- as well as high-pressure spray equipment (MOE < 100). The risk appeared to be acceptable if workers wore chemical resistant clothing, gloves and a half-facepiece respirator with combined dust and gas cartridge. Respirators were not required when using high-pressure hand equipment.

Exposure during incorporation of diluted fipronil product into peatmoss (mushroom casing) could not be estimated due to the absence of an appropriate model. A qualitative assessment of the risk to peatmoss workers indicated the need to wear cotton overalls or equivalent clothing and gloves for occupational protection. If, however, the spray is applied using hand-held equipment, workers will need to wear chemical resistant clothing, elbow-length gloves and a half-face respirator.

Seed treatment is mostly carried out by professional seed treaters in closed systems. Application activities are usually mechanised and do not result in much worker exposure. Seed baggers may be exposed to fipronil dust when handling treated seed. A qualitative risk assessment for farmers who may treat seed on

their farms indicated the need to wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, and a disposable dust mask when using the prepared slurry and bagging treated seeds.

For termite control, fipronil is applied by hand-held equipment, including low-pressure hand wand and soil injection (rodding). There are no exposure data in the PHED for the type of low-pressure hand wands that are used in trenching to create chemical soil barriers (horizontal, vertical or external perimeter) around or under existing building structures. The 'liquid/open pour/termiticide injection' scenario from the PHED was found to be the most suitable surrogate for exposure modelling and contains exposure data only for mixing/loading and application under slab foundation (rodding) and crawl spaces. PHED data suggest that during injection, trenching and rodding methods, chemical resistant clothing and gloves are sufficient to protect pest control operators during application to post-construction soil barriers. The US worker exposure study data for spray probe and injector application indicate a requirement for respiratory protection (a half-facepiece respirator with combined dust and gas cartridge) during spray preparation and application.

Calculating the likely risk to residents occupying houses treated for termite control immediately after treatment indicated that it was acceptable because the air concentrations of fipronil were extremely low.

Pet groomer exposure studies indicated that there is an acceptable risk to workers using Frontline products to treat dogs. Exposure data from these studies indicated the need for gloves when using the spray formulation. Risk from using spot formulation was found to be acceptable even if workers did not wear gloves.

Workers entering treated areas for harvesting or other activities or re-handling treated seed may be exposed to fipronil residues or its degradation products. Safe re-entry/re-handling intervals were calculated for each crop taking into account the amount of fipronil applied and the degradation of fipronil on foliage. The major photolytic metabolite, fipronil-desulfinyl (MB 46513), has repeat-dose toxicity similar to that of the parent compound, resulting in the same end-point for both compounds. Results indicated that, for most post-application activities, no personal protective equipment would be required to be worn once the spray has dried, with a few notable exceptions. For treated brassica, high exposure activities including hand harvesting, irrigation, pruning, topping, tying mature plants were considered to pose unacceptable risks for up to 13 days after application. Hence, a 13-day re-entry interval is proposed. If these activities are required within the 13-day interval then personal protective equipment should be worn so that there is no unacceptable risk posed to the worker. For hand-weeding and transplanting turf, the magnitude of the MOE was considered to be unacceptable for up to 35 days after application. Hence, a 35-day re-entry interval is proposed. If handweeding and transplanting activities need to be performed during the 35-day re-entry interval, personal protective equipment should be worn so that there is no unacceptable risk posed to the worker.

Girdling activities in grapevines is not expected to result in appreciable exposure as fipronil is applied to dormant vines (without leaves) following pruning and prior to budburst and girdling is carried out at bloom time or within two or three weeks of fruit ripening. Similarly, in the case of mushrooms, fipronil is applied at the time of preparation of peatmoss. Since there is no foliage on which fipronil residues could be deposited, there is likely to be minimal dermal or inhalation exposure during mushroom harvesting. Moreover, although mushrooms are harvested manually, picking is usually conducted a few weeks after treatment (normally during spawning) and workers wear gloves to protect the produce (*Australian Mushroom Growers Response to Review of Fipronil*).

## 3.2.9 Safety directions and re-entry intervals/re-handling statements

### SAFETY DIRECTIONS

The occupational health and safety assessment identified a need to revise the currently recommended personal protective equipment for use by persons handling and applying fipronil products and to recommend appropriate personal protective equipment for persons applying the diluted products. Table 9 summarises the outcomes of the OHS assessment of the safety directions for fipronil products.

**Table 9: Outcomes of the OHS assessment of the safety directions**

| OUTCOME | FORMULATION |
|---|---|
| No change | HG BA 0.5 g/kg or less in plastic labyrinth |
| | BA 3.4 g/kg or less in propylene glycol impregnated in cardboard * † |
| | GR 1 g/kg or less |
| | HV SA 100 g/L or less |
| | HV LD 2.5 g/L or less |
| | DU 5 g/kg or less with bentonite PD all strengths * †† |
| | Thiodicarb SC 400 g/L or less with fipronil 80 g/L or less |
| New entry | BA gel 0.5 g/kg or less |
| Amended entry | WG 800 g/L or less |
| | UL 25 g/L or less |
| | SC 500 g/L or less, more than 200 g/L |
| | SC 200 g/L or less, more than 100 g/L |
| | SC 100 g/L or less |
| Deleted entry # | EC 300 g/L or less |
| | WP 10 g/kg or less |
| | HG WP 10 g/kg or less |
| | GB 0.2 g/kg or less |
| | HG BA gel 0.5 g/kg or less |

*Notes:*

** These entries have only been evaluated in terms of sensitisation and the necessity for the 180 statement. The remaining safety directions were not reviewed in either the Toxicology or OHS reports as the entry occurred after the data-call in period for the Fipronil Review.*

*† This entry is expressed as 'BA 0.03 g/station or less in propylene glycol impregnated in cardboard' in the toxicology and OHS reports in Volume 2.*

*†† This entry is expressed as 'DU 5 g/kg or less' in the toxicology and OHS reports in Volume 2.*

*# The current entries for fipronil EC 300 g/L or less, WP 10 g/kg or less, HG WP 10 g/kg or less and GB 0.2 g/kg or less should be deleted as there are no longer any registered products in these categories. The current entry for HG BA gel 0.5 g/kg or less should be deleted, as it is included under the new entry BA gel 0.5 g/kg or less.*

The recommended safety directions from the separate toxicology and OHS assessments have been combined and are provided in Section 4.3.2.

## RE-ENTRY INTERVALS AND RE-ENTRY/RE-HANDLING STATEMENTS

The results of the OCSEH OHS assessment indicated the following re-entry intervals and re-entry/re-handling statements for various crops and agricultural activities:

| | |
|---|---|
| Bananas | 0 day (hand harvesting, stripping, irrigation, weeding mature plants) |
| Brassicas | 0 day (irrigation, scouting, thinning, weeding immature plants)<br>0 day (scouting mature plants)<br>13 days (hand harvesting, irrigation, pruning, topping, tying mature plants) |
| Cotton | 0 day (Irrigation and scouting mature plants)<br>0 day (hand harvesting, pruning, skating) |
| Grapevines | 0 day ((scouting, training, irrigation) |
| Potato | 0 day (hand harvesting) |
| Sorghum | 0 day (irrigation, weeding mature/full foliage plants) |
| Sugarcane | 0 day (scouting mature plants) |
| Turf | 0 day (mowing)<br>35 days (hand weeding, transplanting) |

Re-entry statement for bananas, cotton, mushrooms, pasture, potato, sorghum and sugarcane:

> ‘Do not allow entry into treated areas until spray has dried. If prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and gloves. Clothing must be laundered after each day’s use.’

Re-entry statement for brassicas:

> ‘Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.
>
> Do not perform high exposure activities including hand-harvesting, irrigation, pruning, topping and/or tying mature plants in brassica for 13 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day’s use.’

Re-entry statement for turf:

> ‘Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Do not perform high exposure activities including handweeding and transplanting for 35 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.'

Re-entry statement for fipronil termiticide treated areas:

'Do not enter treated areas until the spray has dried.'

Re-handling statement for seed treated with fipronil products:

'Treated seed should be allowed to dry before re-handling. Wear dust mask when handling treated seed'.

Re-handling statement for animals treated with fipronil spray formulations:

'Animals treated with fipronil spray formulations should not be handled till the spray has dried. If prior handling is required, workers should wear rubber gloves'.

Precautionary statement:

'Human flaggers, if used in aerial spraying operations, must be protected by enclosed cabs'.

### 3.2.10 Exposure mitigation methods

Fipronil and many of its products currently registered in Australia are determined to be hazardous substances (refer Volume 2, OHS report, Appendix II). In accordance with Commonwealth, state and territory hazardous substances legislation, the control measures listed in Appendix II must be instituted where applicable.

## 3.3 Animal safety

The APVMA engaged an external reviewer to assess the published and unpublished animal safety data for fipronil. This included a literature review of information available in the public domain, as well as adverse experience reports provided to the APVMA, and animal safety studies provided by the registrant. The complete literature review and the complete report on the animal safety studies are in Volume 2.

### 3.3.1 Animal safety—literature review

The purpose of the literature review was to summarise the published and unpublished information concerning the safety of fipronil in the target species (dogs and cats), as well as off-label use in non-target species, and to present an assessment of the potential risks. The information was obtained from published and unpublished sources of information, including international databases, scientific publications, web-based peer review (e.g. Veterinary Information Network website), the APVMA Adverse Experience Reporting Program and also information provided by the registrant regarding global suspected adverse drug experience (ADE) reports.

In Australia, fipronil was first registered as a veterinary pesticide in 1995 as Frontline Spray, with the spot-on forms of fipronil (Top Spot) registered from 1996 onwards for dogs, cats, puppies and kittens. Frontline spray contains 2.5 g/L fipronil. The topical spot-on contains 100 g/L fipronil. An insect growth regulator, (S)-methoprene [90 g/L for dogs or 120 g/L for cats], has also been included with several of the products containing fipronil, for example Frontline Plus for dogs or cats and Startgard Plus for puppies or kittens.

## SUMMARY OF PUBLICLY AVAILABLE INFORMATION AND INTERPRETATIONS

Unless indicated otherwise, the cited information has been sourced from summaries or other information in the public domain, and not from examination of the original unpublished reports.

### *Mechanism of action*

Fipronil [5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-fluoromethylsulfinyl pyrazole] is a second-generation phenylpyrazole insecticide. The principle mechanism of action is against the GABA receptor-chloride complex. Ligand-gated chloride channels, such as GABA, act to inhibit excitable membranes. Blockage of the GABA-gated chloride channels by fipronil reduces neuronal inhibition and leads to hyper-excitation of the central nervous system, convulsions and death (Bloomquist 1996,2003; Zhao et al. 2003; Zhao et al. 2004).

Ligand-gated GABA chloride channels are also essential to vertebrate nervous function, but fipronil appears to be selective for insecticidal forms of this membrane-bound protein complex (Bloomquist 2003; Zhao et al. 2003). The sensitivity of insects to fipronil is 700–1300 times higher than that of rats (Zhao et al. 2004).

### *Metabolism of fipronil*

The major metabolite of fipronil in vertebrates and invertebrates appears to be fipronil sulfone (Hainzl and Casida 1996; Hainzl et al. 1998). On plants and in soils, fipronil undergoes a photoextrusion reaction, yielding a desulfinyl derivative (Hainzl and Casida 1996). There have been limited studies of the degradation of fipronil on the surface (skin) of domestic species, particularly dogs and cats. It has been reported that basic conditions (pH > 7) and increased temperatures will induce hydrolysis of fipronil (Ramesh and Balasubramanian 1999), conditions that may occur on the skin surface of mammals.

The selective toxicity of fipronil will therefore depend on the relative rate of conversion to the more persistent and less selective sulfone metabolite and desulfinyl photoproduct (Hainzl et al. 1998). The desulfinyl photoproduct, in particular, has a tenfold greater selectivity for mammalian GABA chloride channels than the parent compound (Hainzl and Casida 1996). No directly applicable data are available on the influence of degradation products on the toxicity of fipronil applied to target animals.

### *Oral toxicity*

The primary initial studies that investigated the oral toxicity of fipronil examined administration of fipronil to laboratory animal species, as part of the human toxicological studies and not target or non-target animal safety. The results of the toxicological studies are used to determine the hazard profile of the product for human exposure, to set first aid instructions and safety directions, and to set acceptable daily intakes and maximum residue limits when the products are used on food commodities.

Following oral administration of fipronil at single doses of 25–200 mg/kg bw (mice), 25–200 mg/kg bw (rats) or daily doses of 75 mg/kg bw for 5 days in rats, acute toxicity studies showed a dose-dependent appearance of neurological signs, including tremors, gait abnormalities and seizures in laboratory animals (Gardner 1988a; Mondot and Dange 1995; Ray 1997). Some bioaccumulation of the test material may occur in laboratory species (Ray 1997), although this is unlikely to be a potential risk to target animals when used according to label directions.

Short-term oral toxicity studies in rats and mice dosed daily with fipronil at levels up to 55 mg/kg bw for 4 weeks, up to and over 22 mg/kg bw for 6 weeks, or up to 24 mg/kg for 13 weeks also revealed dose-dependent toxicity of orally administered fipronil, although obvious signs of gastrointestinal (inappetence and weight loss) and neurological signs (depression, lethargy and/or death) did not occur until higher dose rates with mortality prominent at the highest doses administered (Broadmeadow 1991; Holmes 1990; Holmes 1991a; Peters et al. 1990). The liver and thyroid were the main organs undergoing histological changes in response to short term (4–13 wks) fipronil dosing and, as this did produce overt clinical signs at lower dose rates (< 5 mg/kg/day), a NOAEL could not be determined.

In Beagle dogs, short term oral toxicity studies also reported toxic effects at the higher dose rates used, particularly 10 mg/kg/day for 13 weeks where neurological and gastrointestinal signs were observed (Holmes 1991b). The NOAEL was 0.5 mg/kg/day. Oral administration of fipronil for one year revealed neurological signs when higher dose rates were administered (> 1 mg/kg/day) and a NOAEL of between 0.2–0.3 mg/kg/day by oral administration was calculated for the dog (Holmes 1992, 1993). Since one female dog did exhibit possible neurological signs (over-activity) when dosed at 0.2 mg/kg/day, a ‘safe’ daily dose of fipronil may be less than this suggested NOAEL.

### *Neurotoxicity*

The potential for fipronil to induce specific neurotoxicity in target and non-target species has also been reported. Acute neurotoxicity studies in the rat following single oral administration of fipronil at levels up to 25 mg/kg bw reported a NOAEL of 2.5 mg/kg with clinical signs reverting to normal by 14 days (Hughes 1997). A second study with single oral administration of fipronil at levels up to 50 mg/kg bw reported a NOAEL of 0.5 mg/kg, based on histopathology and clinical signs up to 16 days after treatment (Gill et al. 1993), while a longer study (fipronil administered orally at levels up to 11 mg/kg bw for 13 weeks) found a NOAEL of 0.3 mg/kg for neurotoxicity in the rat (Driscoll and Hurley 1993). A limited study in the dog reported that 20 mg/kg/day orally induced neurotoxicity from 5–13 days after commencement of treatment and food consumption decreased from 1–2 days after commencement of treatment (Holmes 1991b). These signs resolved within 12 days of cessation of treatment and it was concluded that clinical signs resulted from systemic pharmacological modulation, which disappeared as the fipronil was eliminated from the body.

Recommended application intervals for fipronil veterinary products are as follows: Spray: up to 12 weeks for fleas on dogs and 8 weeks for fleas on cats; monthly for FAD in cats and dogs and sarcoptic mange in dogs; up to 3 weeks for paralysis ticks; up to 4 weeks for brown dog ticks. An application interval for the treatment of lice on dogs and cats is not specified. Dog spot ons: monthly for fleas, FAD, brown dog tick and sarcoptic mange; fortnightly for paralysis tick; and as directed for lice. Cat spot-ons: monthly for fleas and FAD, and as directed for lice. The dose rate equates to a possible 13.4 mg fipronil/kg bw for spot-on products and 15.0 mg fipronil/kg bw for fipronil spray, assuming application to the lowest bodyweight in the dosing range, at each dosing interval. The potential for systemic toxicity will depend on the bioavailability of active ingredient,

either by ingestion or transdermal penetration. This review was particularly concerned with safety of fipronil under normal conditions of use (topical application). However, ingestion of fipronil concentrate (packaged to dispense 13.4 mg/kg per tube) may approach acute toxic doses (75 mg/kg in mice), particularly if the entire contents (between three and six tubes) of a package are ingested (Mondot and Dange 1995). This would not be considered normal use and would fall under inadvertent toxicity. Some ingestion may also occur following licking and grooming of the site of application, despite the relatively low accessibility of this site (normally the back of the neck).

Significant toxicity, particularly neurological signs, was reported in the toxicity studies in dogs after daily oral administration of fipronil at 10 mg/kg/day for 13 weeks, while inappetence and poor condition was noted at 2 mg/kg/day (Holmes 1991b). Since total absorption of radiolabelled fipronil applied topically to rats was less than 1% over 24 hours, it would appear highly unlikely that application of a single dose of the commercially-available fipronil formulations would approach significantly toxic doses (2+ mg/kg/day), even in the cat (assuming similar toxicological effects) with more fastidious grooming habits. Yet a closer inspection of some of the ADEs reported for cats under 'neurological' signs were listed as salivation/drooling and mild inappetence, which may be secondary to grooming the site of application. It is difficult to differentiate, particularly in the cat, if these reactions are a specific toxicosis or a local reaction of the oral mucosa to an ingested foreign substance.

### *Endocrine disruption*

The effects of fipronil on endocrine function were studied in the rat since some disruption of endocrine function is possible (Bloomquist 1996; Colborn 1998; Davis et al. 1996; Davis et al. 2000; McCarthy 1995). Pregnancy rates were reduced at high doses (280 mg/kg) of fipronil (Frontline Top-Spot) applied as a single dose topically to rats, while hormonal changes were found at lower doses (70 mg/kg) (Ohi et al. 2004). These doses are substantially higher than what may be expected following topical application and appear to suggest that reproductive and endocrine function would be unlikely to be disrupted with normal use of fipronil-containing products. Safety studies in the dog (DOG PR&D 0020201; Godin and Alva 2000b) and cat (CAT PR&D 0020301; Godin and Alva 2000a) provided by the applicant have shown that fipronil can be applied safely to these animals during pregnancy and lactation, with no adverse effects to either parent or offspring. Similarly, in trials with weanlings and juveniles, there were no significant adverse effects observed in this relatively vulnerable group and therefore fipronil could be considered safe to use in younger animals, including weanlings.

### *Skin absorption*

Fipronil products registered for use in dogs and cats are formulated for topical application. The relative proportion of radiolabelled fipronil that is absorbed through the skin appeared to decrease with increasing dose rate (Cheng 1996), which suggested that pathways of transdermal absorption may be saturable. The bioavailability of topically-applied fipronil is generally accepted as $\leq$ 5% (Brayden, 2003) due to limited permeability through the stratum corneum (Birckel et al. 1996; Cochet et al. 1997). *In vivo* studies in the rat showed that absorption of a suspension of radiolabelled fipronil decreased with increasing dose and that absorption was saturated when 48.5 mg/rat (194.0 mg/kg if the rat weighed 250 g) was applied. The proportion of the applied dose that had penetrated the different membranes also varied with species and time, with relatively less penetration after application of a 4.0 g/L formulation than after 0.2 g/L. It was reported that less than 1% of the applied dose was absorbed, but up to 3.3% (following application of 8.35

mg/rat) was found left on the skin after the first 24 hours (Cheng 1995). This equates to 0.13 mg/kg (1%) absorbed following a single topical administration to dogs at recommended dose rates and 0.43 mg/kg (3.3%) remaining on the skin. These results agreed with studies using radiolabelled fipronil *in vivo* to demonstrate that percutaneous passage of fipronil was low (Cochet et al. 1997), similar to the cat (Birckel et al. 1996).

A NOAEL for oral toxicity of fipronil in the dog of 0.2 mg/kg/day (calculated from daily oral administration for one year (Holmes 1992, 1993)) is substantially higher than a possible 0.13 mg/kg (or 0.15 mg/kg of spray formulation) every two to four weeks. This level of exposure is also considerably less than the dermal $LD_{50}$ for fipronil applied in distilled water to rats (> 2000 mg/kg in both males and females), while in rabbits the dermal $LD_{50}$ for test material moistened with corn oil was 354 mg/kg for the two sexes combined. Neither clinical signs of toxicity nor deaths were seen in rats. In rabbits, fipronil induced deaths and one or more clinical signs of toxicity including convulsions, sluggishness, salivation, spasms, tremors, hyperactivity, diarrhoea, emaciation, and perioral and perinasal red discolouration in all groups except that at the lowest dose (100 mg/kg). Delays in the appearance of signs of toxicity and death were noted at all doses except the lowest. In particular, convulsions were not observed until days 3–9 after treatment, and some animals did not die until days 11–14 (Gardner 1988b; Myers and Christopher 1992).

It would appear, in the limited number of dogs used in these studies (Birckel et al. 1996; Cochet at al. 1997) that fipronil, applied at recommended dose rates and dose intervals, would be highly unlikely to be absorbed in sufficient quantities to induce signs of systemic toxicosis (i.e. neurological and gastrointestinal signs) in the normal dog and cat and, importantly, suggests that topical application of marketed formulations of fipronil-containing products is safe in the dog and the cat.

### *Transdermal penetration of fipronil and/or metabolites*

Topically-applied fipronil is sequestered by sebaceous glands and is gradually released over a two month period (Dryden et al. 2000). The bioavailability of topically-applied fipronil is generally accepted as $\leq 5\%$ in dogs and cats (Brayden, 2003) due to limited permeability through the stratum corneum (Birckel et al. 1996; Cochet et al. 1997).

Limited information is available regarding transdermal movement of fipronil and/or metabolites through dogs and cats. Radiolabelled [$^{14}$C]fipronil administered to dogs was investigated using auto-historadiography for up to 56 days after topical application. The radioactivity was found to spread down to the lumbar region and penetrate into the stratum corneum, pilo-sebaceous units and the viable epidermis. No radioactivity was found in the dermal of hypodermal layers, which was suggested to represent low percutaneous passage of fipronil in the dog (Cochet et al. 1997). A similar study in the cat also found that topically applied fipronil has low percutaneous penetration and was primarily found in the stratum corneum and sebaceous glands (Birckel et al. 1996).

### *Toxicity in cats*

The reviewer was unable to find information relating to fipronil toxicity and toxicological studies specifically in the cat, although the toxicological studies were conducted for human safety and these are not usually conducted in cats. It is noteworthy, however, that obvious species differences have been found in transdermal penetration of fipronil (rabbit *versus* rat) (Birckel et al. 1996) and further studies are strongly

recommended to quantify fipronil movement through feline skin. *In vitro* studies in human, rabbit and rat skin showed that the extent of penetration increased with time across species (Walters and Brain 1990). It was interesting that fipronil appeared to penetrate rabbit skin up to a tenfold order of magnitude higher than rat skin and this may be a predisposing factor to toxicity in this species. It was also noted that there were no *in vitro* studies in either dog or cat skin, despite the reported species differences in transdermal fipronil penetration.

### *Toxicity in young animals*

An additional factor that was apparent in reported toxicological studies relating to topical application of fipronil is that generally young healthy animals, or skin from healthy animals for *in vitro* studies, were used. A survey of published studies relating to efficacy of fipronil-containing products reveals that it is applied to animals to control ectoparasites, which are often associated with skin damage, such as flea allergy dermatitis (Hutchinson et al. 1998; Cadiergues et al. 2001; Medleau et al. 2002; Medleau et al. 2003). Damage to the epidermis, particularly the stratum corneum, will dramatically reduce the barrier function of skin (Roberts et al. 2002), which may then permit significantly greater amount of active ingredient and/or vehicle through to the systemic circulation. The potential toxicity of fipronil-containing products applied to damaged skin has not, to the reviewer's knowledge, been specifically assessed in any species, most importantly the target species.

### *Toxicity of metabolites*

Specific toxicity resulting from metabolites of fipronil is difficult to determine because it is uncertain how much degradation of the parent compound will occur when applied to animal skin. Basic conditions (pH > 7) and increased temperatures will induce hydrolysis of fipronil (Ramesh and Balasubramanian 1999), and these conditions may occur on the skin surface of mammals. The influence of sunlight to induce degradation of fipronil to the desulfinyl derivative (Hainzl and Casida 1996) following topical application is also uncertain. However, since transdermal passage of radiolabelled fipronil (which will include any metabolites formed) is less 5%, it is reasonable to assume that systemic penetration of any metabolites formed would be less than this. Furthermore, the recovery of topically applied radiolabelled fipronil desulfinyl (in 1% carboxymethylcellulose) was 93–103%, with the majority of this (90–102%) being present in the skin wash, suggesting that much of an applied dose resides on or within the skin (Cheng 1996). It would therefore be unlikely that any significant toxicity or specific neurotoxicity would result from degradation of fipronil after topical administration, despite the reported tenfold greater selectivity for mammalian GABA chloride channels than the parent compound (Hainzl and Casida 1996). It was noted, however, that insufficient information exists concerning the degradation of fipronil *in vivo* and the potential toxicity of metabolites to the target species.

### *Published studies investigating the efficacy of fipronil-containing products*

It is beyond the scope of this review to investigate the efficacy of fipronil-containing products in the dog and cat, however some of the published studies of efficacy may provide 'field trial-type' information where the product is applied under different conditions to different animal breeds, while laboratory-based efficacy studies are usually under strictly controlled conditions and typically use a single breed (e.g. beagle for dog studies). On reviewing the published efficacy studies it was, however, difficult to assess local reactions because many of the animals had pre-existing skin conditions caused by the parasites and treatment with

fipronil resolved the condition (Curtis 1996; Hutchinson et al. 1998; Nuttall et al. 1998; Bordeau and Hubert 2000; Dryden et al. 2000; Ritzhaupt et al. 2000a,b; Cadiergues et al. 2001; Jacobs et al. 2001; Mehlhorn et al. 2001; Moyses and Gfeller, 2001; Medleau et al. 2002; Pollmeier et al. 2002; Medleau et al. 2003; Curtis 2004; Pollmeier et al. 2004).

## ADVERSE DRUG EXPERIENCE REPORTS FOR FIPRONIL IN DOGS AND CATS

Adverse drug experiences (ADEs) are a difficult set of data to define because they may not represent the entire picture and cannot be used to calculate an overall incidence because the number of unreported ADEs is always unknown. They can also be inconclusive due to any number of confounding factors, such as concurrent drug administration, underlying disease processes (diagnosed or subclinical) and the variable ability of pet owners and veterinarians to recognise an ADE. Two major benefits in the reporting of ADEs are that an increased frequency of reporting may highlight previously unknown problems with a newly registered pharmaceutical as part of an ongoing pharmacovigilance process and, secondly, the reporting of ADEs may also amplify non-significant clinical observations noted in smaller clinical trials.

### *ADEs in Australia*

The information for ADEs in Australia was supplied from the APVMA database (1996–2003). In the following tables, ADEs were grouped into broad categories of clinical signs for convenience and to concentrate an understanding of specific problems associated with fipronil use in the dog and cat.

**Table 10: ADEs reported for use of fipronil-containing products in cats in Australia (1996-2003)**

| ADE | CATS | | |
|---|---|---|---|
| | FRONTLINE TOP SPOT | FRONTLINE PLUS* | FRONTLINE SPRAY |
| Alopecia ± hair colour change | 23 | 14 | 0 |
| Alopecia ± pruritus ± erythema | 46 | 26 | 1 |
| Neurological | 23 | 9 | 2 |
| Gastrointestinal | 3 | 0 | 1 |

** a spot on formulation containing fipronil and (S)-methoprene*

The most frequently reported ADEs in the cat was for hair loss (alopecia), with or without associated pruritus and erythema. This primarily occurred at or around the application site. Many signs observed could be those of local irritation or contact-type dermatitis. The signs classed as neurological included inappetence, lethargy and salivating. Some animals were reported as distressed and/or displaying intense pruritus—these are difficult to separate from behavioural responses associated with intense local skin reactions. Gastrointestinal signs that were reported were primarily vomiting.

It was noted that some of the ADEs reported for Frontline Plus included comment from owners that Top Spot had been previously used on the animal with no adverse effects. The reviewer acknowledges that the number of reported ADEs for a newly released product increases and peaks in the first two years after release, the so-called ‘Weber Effect’ (Wallenstein and Fife 2001; Hartnell and Wilson 2004). As such, it is

difficult to comment on the relevance of prior use of fipronil-containing formulations on subsequent adverse effects.

It was also noted that the two reports of neurological signs following the use of the spray may have been related to placing the treated (wet) animal into an enclosed space. The fumes arising from the fipronil spray on the fur may have created an inadvertent inhalation dose of fipronil, although alcohol as the carrier agent in the spray may also be implicated. It was noted that the label for the spray formulation contained a warning to treat the pet either outside or in a well-ventilated room, which should avoid this potential ADE.

**Table 11: ADEs reported for use of fipronil-containing products in dogs in Australia (1996-2003)**

| ADE | DOGS | | |
|---|---|---|---|
| | FRONTLINE TOP SPOT | FRONTLINE PLUS* | FRONTLINE SPRAY |
| Skin reaction | 156 | 57 | 23 |
| Neurological | 23 | 15 | 0 |
| Gastrointestinal | 9 | 5 | 0 |
| Ocular | 0 | 0 | 1 |

Similarly to cats, skin reactions were the highest reported ADEs for fipronil-containing products in dogs. There did not appear as many obvious reports of alopecia alone, with frequent pruritus and erythema associated with the area of application. Up to half of the skin reactions were quite severe and acute moist dermatitis ('hot spot') was reported. This is possibly secondary to self-trauma. It is noted that self-trauma or primary skin reactions may reduce the integrity of the stratum corneum and increase the systemic absorption of fipronil (Roberts et al. 2002).

Many of the skin reactions occurred immediately or soon after application, establishing a link between fipronil and skin irritation. There were some reports of dogs avoiding subsequent application of Top Spot. Neurological clinical signs included ataxia, lethargy and two instance of biting or aggression. Gastrointestinal signs included vomiting and diarrhoea. It is possible that gastrointestinal problems were induced following ingestion of the concentrate (after chewing the application tube); whether or not these arose from specific direct irritation of gastrointestinal mucosa or a reaction to fipronil *per se* has not been established.

Off-label use of fipronil

A number of reports of ADEs following 'off-label' use were also noted, particularly in rabbits. There were ADE reports of 32 rabbits dying following application of fipronil concentrate or spray, whereas there were reports of only 13 animals recovering. All displayed neurological signs of severe lethargy, depression and inappetence. There was only one published report (Webster 1999) of this potential problem in using fipronil in rabbits and this was cited in many instances throughout the literature.

There was also one report of nine guinea pigs exhibiting ADEs, with six deaths occurring after displaying neurological signs.

Efficacy issues

It is beyond the scope of this review to examine efficacy of fipronil containing products. However, a substantial number of the ADEs reported were related to lack of efficacy, particularly against paralysis ticks. There were 15 reports of fipronil spray not killing ticks and at least 25 reports of live ticks found on dogs following application of fipronil concentrate. Several of these animals subsequently died as a result of tick paralysis.

The 'ADEs' reported for animals concurrently suffering from tick paralysis appear to result primarily from the tick envenomation. These clinical signs include depression, paralysis or paresis (weakness), respiratory depression, vomiting and death.

It would appear that the majority, if not all, the clinical signs reported as ADEs with concurrent attachment of *Ixodes holocyclus* probably resulted from tick venom and not a reaction to fipronil. As such, these were not considered by the reviewer as ADEs and were not included in the above tables. It should be noted that the label claim is for control of ticks, not prevention of attachment, and the label contains a warning to this effect.

### *ADEs in USA*

A search of the Veterinary Information Network (VIN) website (a restricted information network for veterinarians and veterinary specialists) revealed several ADEs that were consistent with ADEs reported in Australia.

### *Global ADE reports*

The registrant presented a comprehensive summary of suspected ADEs to fipronil in animals reported globally for a four-year period between 2000 and 2003. The reporting incidence of ADEs in the cat and dog was low (< 0.001%) for spray and spot-on (and spot-on plus) products. This would appear within reasonable acceptable limits for this extensively used group of products. The reporting incidence was calculated on the number of doses sold. Of the 4534 ADEs reported, 2847 may potentially be considered as consistent with hypersensitivity, with cutaneous reactions (86.3%) forming the greater majority of the latter. The global incidence of ADEs to fipronil in dogs and cats is not common.

The total incidence within Australia (< 0.0024%) was 2.7 times higher than globally reported ADEs. Similarly, the majority of ADEs reported in target species in Australia were related to cutaneous signs (75.6%). While still low, it is concerning that the incidence of ADE reports is higher in Australia and the registrant did not offer any reason for this disparity, although the low reporting incidence and variability of ADEs may account for this difference.

Studies in laboratory species have demonstrated that fipronil has the potential to induce mild to moderate cutaneous irritancy. While cutaneous reactions are unlikely to be life-threatening, they may be of concern to owners, particularly if they are not advised in the labelling that skin irritation and/or damage can occur.

The registrant did not include ADEs involving paralysis ticks in the overall ADEs reported for fipronil in Australia. This appears justified because it is difficult to separate the clinical signs of tick paralysis from any possible neurological clinical signs that may result from fipronil toxicosis. It is the reviewer's opinion that the

neurological signs described in the ADE reports are consistent with tick paralysis alone and these ADE reports are more accurately termed 'lack of efficacy' reports.

### *Discussion of adverse drug experiences*

Skin reactions appear to be the most common ADE reported for fipronil in dogs and cats both globally and in Australia. Fipronil moistened with corn oil caused slight dermal irritation to New Zealand white rabbits after a 4-hour application to intact skin, yet this did not occur if fipronil was moistened with water (Liggett 1988a; Myers and Christopher 1993). Using the Buehler method, fipronil (30% w/v in paraffin oil) produced no sign of dermal sensitization in guinea pigs (Smith 1990), however using the method of Magnussen and Kligman, it was reported that fipronil (10% in propylene glycol) was a mild or weak skin sensitiser (Johnson 1993). The APVMA notes that the OCSEH assessed these sensitisation studies as part of the review of fipronil and concluded that fipronil was not a skin sensitiser in guinea pigs (see Section 3.1.1, 'Acute toxicity studies', page 9). It cannot be discounted that the vehicle may contribute to the dermal response to fipronil-containing products, either directly or related to concentration of active ingredient in the vehicle (the maximum flux ($J_{max}$) or driving force for transdermal drug penetration is dependent on concentration, and therefore solubility, of the drug in the vehicle (Roberts et al. 2002). No signs of dermal irritation were seen in rabbits when the metabolite, fipronil sulphone, was applied to the skin at a single dose of 0.5 mg moistened with distilled water for 4 hours (Liggett, 1988b).

Indications from published and anecdotal reports suggest that fipronil-containing products can induce cutaneous reactions in some dogs and cats. These reactions, ranging from alopecia to acute moist dermatitis, are unlikely to cause serious signs of disease in affected animals, but may cause distress to owners and the affected animals. This would be particularly so in breeders and owners of show or competition animals where perturbations in the skin may preclude entering in competition. A further consideration for cutaneous reactions is that damage to the skin, either directly or secondary to pruritus and self-trauma, may predispose the animal to enhanced systemic absorption of fipronil as the barrier function of the skin is compromised. Fipronil resides within the openings of appendages (hair follicles and possibly sweat glands) and damage or removal of follicles and, particularly, the stratum corneum (outermost skin layer), removes the primary barrier to drug movement through skin. A significantly greater potential for increased systemic concentrations of fipronil and its metabolites is possible if fipronil-containing products are applied to skin damaged in any way. However, the still relatively low percutaneous penetration and wide margin of safety are consistent with no reports of toxicity attributable to enhanced passage of fipronil-containing products through damaged or inflamed skin.

Neurological signs, including inappetence, lethargy and salivation, were the second most frequent ADE reported in cats and dogs within Australia. This is a difficult category to evaluate because of overlap between true neurological signs and animals exhibiting excitation or anxiety secondary to fipronil application. For example, some dogs are reported to resent topical application of fipronil-containing products, while other may show apparent neurological signs (e.g. shaking, anxiety, intense scratching) if a local skin reaction is upsetting the animal. Similarly, cats are known to froth from the mouth and become distressed if certain foreign substances contact oral mucosa, which can readily occur if the cat ingests recently applied fipronil during grooming. Close examination of ADE reports suggest that many 'neurological' signs were probably local reactions because:

- the classic neurological signs of fipronil toxicity, including fitting, hypo-activity, ataxia, tremors and lack of vision, were not reported
- many of the reactions occurred soon after topical application and true neurological signs were reported to appear after a variable period of time (up to three days in rabbits) as the drug penetrated through the skin and into the systemic circulation.

However, there were some reports of ADEs that do appear to be true neurological signs, particularly animals exhibiting aggression and marked in-coordination. Some guidelines on reporting ADEs for fipronil may be useful in future to assist distinction between specific clinical signs. For example, failure to prevent paralysis tick attachment is not a neurological sign *per se*.

A further problem with evaluation of neurological ADE reports in Australia is that many of the reports were associated with concurrent effects of paralysis tick. There is some overlap between the clinical signs observed in both fipronil toxicity and tick paralysis, particularly hypo-activity, hind leg splay and increased respiratory effort. It is the strong opinion of the reviewer that the majority, if not all, neurological signs reported as ADEs when the animal was concurrently suffering from tick paralysis were related to tick venom and not fipronil. The reports of ADE are therefore best considered as lack of efficacy in controlling the tick.

### 3.3.2 Animal safety studies

The assessment considered animal safety data provided by the applicant for the review.

A total of thirteen safety studies in dogs and cats were provided for assessment. These included

- studies conducted with the fipronil spray formulation applied at up to five times the recommended rate and multiple times at 28 day intervals to dogs and cats, and puppies and kittens, including nursing puppies and kittens
- a study conducted with the spray formulation applied at the upper recommended rate to unweaned kittens and their queens
- studies conducted with the fipronil spot-on formulation applied at up to five times the recommended rate and multiple times at 28 day intervals to juvenile dogs and cats
- studies conducted with the fipronil plus methoprene spot-on formulation applied at up to five times the recommended rate and multiple times at 28 day intervals to juvenile dogs and cats
- studies conducted with the fipronil plus methoprene spot-on formulation applied at up to three times the recommended rate and multiple times to adult female dogs and cats during pregnancy and lactation.

#### DISCUSSION OF SAFETY STUDIES

All of the studies were, in general, conceived and performed well. The reports were thorough and comprehensive. The studies used a thorough and wide range of parameters, including haematology and clinical chemistry, to monitor animal health. However, there were several issues in the studies that were of concern to the reviewer, including: the majority of the animals used in the safety studies were of the same or similar breed; all animals in these safety studies could be considered as young animals; a large number of the animals in many of the studies had some underlying evidence of histopathology in the skin which made it

difficult to determine whether there are any statistically significant localised effects following topical application of fipronil-containing products; and there were relatively few numbers in each treatment group in most of the studies reviewed, although this is acceptable for pen studies of this nature.

One primary concern regarding the safety of fipronil-containing products was the effect on the site of application following topical application. This was difficult to verify statistically due to relatively small numbers of animals in each treatment group and an underlying incidence of histopathology, albeit minor, in test animals. It was also evident that local irritation or reaction to treatment may not be dose related and, most importantly, may also be associated with the vehicle and not the active ingredient. Two studies did not investigate histopathological changes following application. However, there was one report of alopecia following application of the vehicle, although it was apparent from reported clinical observations that some dogs were pruritic after topical application of the spot-on. This was consistent with at least one study where the treatment appeared to induce local inflammatory changes over the site of application.

In addition to pruritus, there may be some incidence of neurological signs following topical application of fipronil. Three cats displayed nervousness or aggression following administration of fipronil spray, although the report summary suggested that this was not related to treatment. One concern with topical application of any spray is the potential for aerosol production and inadvertent inhalation. Absorption of fipronil into mucosa is higher than through skin and it is possible that the cats may be demonstrating systemic signs of fipronil toxicosis, but the possibility of the cats reacting to the alcohol in the spray or to the mere act of being sprayed cannot be determined from the studies presented to date. Again, greater numbers of animals in the study may confirm or reject this possibility. Neurological signs in dogs from the safety studies appeared limited to anxiety related to pruritus.

An overall conclusion from the safety studies provided is that fipronil-containing products appeared safe when applied topically to dogs and cats. This conclusion was strengthened by the safety studies in young and nursing animals where a higher incidence of ADEs may be expected.

There does, however, appear to be a possibility of local skin reactions following treatment. Several animals in the safety studies exhibited reactions which included alopecia, irritation or pruritus, scurf or dandruff appearing and underlying histopathological reactions. Effects of fipronil-containing products, particularly at the site of application, may not be dose related and may represent individual sensitivity to the active constituent and/or the vehicle. Local skin reactions are unlikely to endanger the overall health of the animal but may be of concern to owners.

To confirm or reject a definitive link between fipronil (and/or the vehicle) and local skin reactions, it would be necessary to undertake larger trials using animals ranging in breed, gender and age. (Field efficacy trials may be able to provide some supporting information on this issue.) In addition, continued assessment of the incidence of local skin reactions in ADE reports as part of pharmacovigilance procedures is warranted.

### 3.3.3 Conclusions

A close examination of the published and unpublished information concerning fipronil use in dogs and cats would suggest that fipronil-containing products are generally safe to use in the healthy target species at recommended dose rates and route of administration. Extensive studies in target and non-target species show that NOAEL figures, calculated from daily oral administration of fipronil to laboratory test species, were

significantly higher than would normally be administered topically on a two- to four-weekly basis to target animals. Information supplied by the registrant on global and Australian ADE reports shows a particularly low incidence of problems encountered in the target species, dogs and cats, when used according to manufacturer's recommendations. There were, however, several areas of concern in the use of fipronil-containing products that should be addressed, either by changes to product labelling or in advice to veterinarians when dispensing this product:

- Individual variation in response to fipronil is to be expected and some differences in tolerances or reactions to fipronil should preclude use of fipronil-containing products in that individual. This was evident when some animals reacted to Frontline Plus yet not with prior use of Frontline Top Spot. The extent and incidence of individual variation in response to fipronil-containing products could not have been predicted from the published and unpublished studies in dogs because a single breed (beagles) was used and this may not be representative of all breeds. More importantly, a single breed of dog may also not be representative of transdermal drug movement in all breeds. However, it is also noted that the reporting incidence is very low, so the chances of seeing a response in the studies may also be expected to be low.
- There was no information or studies into transdermal movement of fipronil through non-normal skin, such as occurs during flea allergy dermatitis or secondary to pruritus. This may contribute to the incidence of 'individual variation' or unexpected toxicity to fipronil. It is recommended that care be taken when administering fipronil to severely excoriated skin and it would be considered good veterinary practice to treat damaged skin conventionally and avoid application of topical anti-parasiticides to the damaged regions.
- While it is appreciated that the global and Australian incidence of cutaneous ADEs is low, there appears to be a real and characteristic reaction to fipronil-containing products in certain animals (i.e. alopecia, pruritus and erythema). This should be noted as a possible adverse reaction in product labelling, particularly for show or competition animals.
- The $LD_{50}$ for fipronil by the inhalation route is substantially lower than for oral administration (Cracknell 1991; Gardner 1988a; Mondot and Dange 1995; Nachreiner 1995). It is strongly recommended that there be some warning to avoid placing animals that have been treated with the spray formulation into enclosed spaces until the coat is dry. Inhalation of fipronil fumes in an enclosed space could contribute to toxicological effects, although the alcohol base for the spray may also be implicated in adverse effects. It is noted that the label contains a warning to treat the pet outside or in a well-ventilated room.
- It is recommended to use fipronil-containing products according to the label directions. This particularly applies to non-target species, such as rabbits and guinea pigs. In fact, it is strongly recommended NOT to use fipronil-containing products in rabbits or guinea pigs. It is noted that since 1993, all Frontline Spray and Frontline Plus products now carry label warnings against using the products in rabbits: 'DO NOT USE IN RABBITS'. However, not all the Frontline Top Spot products have this label warning.

## 3.4 Overseas regulatory status

Products containing fipronil for use in agriculture or on animals are registered worldwide.

### 3.4.1 US EPA

Fipronil was first registered for animal health in the United States in 1996 as Frontline Spray, containing 0.29% w/w fipronil, and Frontline TopSpot, containing 9.7% fipronil w/w.

The US EPA has approved fipronil products for agricultural and domestic (veterinary and home garden) uses. Registered domestic fipronil products are approved for use on cats and dogs for flea control and on turf to control fire ants. The US EPA conducted an aggregate dietary exposure estimate for fipronil and concluded that chronic dietary exposure to fipronil residues from both primary and secondary sources, as a result of its use on field corn, potatoes, rice and cotton does not represent a significant risk to any segment of the population.[14] The US EPA also approved agricultural fipronil products for use on potato and sweet potato in August 2007 and for use on pine seedling in June 2007.[15]

In the United States, the Department of Pesticide Regulation (Californian Environmental Protection Agency) initiated a review of registered pesticide products containing fipronil in November 2001 based on human health concerns. Review findings have not yet been released.

In July 2004, the US EPA approved requests submitted by Bayer CropScience to voluntarily cancel the registrations of certain pesticide products containing fipronil for use on rice or rice seed. Any distribution, sale or use of the products subject to this cancellation order was only permitted in accordance with the terms of the existing stocks provision of this cancellation order.

### 3.4.2 European Union

The European Food Safety Authority (EFSA), the lead agency in the European Union's pesticide review process, completed a re-evaluation of fipronil and its products in 2006.[16] In 2007 the European Commission Health and Consumer Protection Directorate-General reviewed the resulting report and additional data in order to ascertain if fipronil should be included in Annex I of Directive 91/414/EEC. The Directive provides for the establishment of a positive list of active substances (Annex I) that have been shown to be without unacceptable risk to people or the environment. The positive list of active substances are authorised for use in plant protection products within the community. The 2007 review[17] concluded that the available data supported use of fipronil as a seed dressing on sunflower and maize. The overall conclusion was that fipronil be included in Annex I of Directive 91/414/EEC for use as a seed dressing.

---

[14] US EPA 2007, Fipronil; Pesticide Tolerances. 40 CFR Part 180 [EPA-HQ-OPP-2005-0206; FRL-8142-6] Federal Register).

[15] US EPA 2007, *Multi-Year Workplan for Reregistration of Conventional Pesticides – Completions for Fiscal Year 2007*. Office of Pesticide Programs.

[16] EFSA 2006, 'Conclusion on the peer review of fipronil', in *Summary of the EFSA Scientific Report (2006)* 65, 1–110, '

[17] EC 2007,' Review report for the active substance of fipronil finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 16 March 2007 in view of the inclusion of fipronil in Annex I of Directive 91/414/EEC. European Commission'.

In 2007, the United Kingdom (UK) published a revocation notice for fipronil agricultural products that did not comply with the specific condition for fipronil's inclusion in Annex I of Directive 91/414/EEC: 'only uses as insecticide for use as seed treatment may be authorised'.

### 3.4.3 AFSSA/AFSSE: Agence Française de Sécurité Sanitaire des Aliments (French Food Health Safety Agency) / Agence Française de Sécurité Sanitaire Environmentale (French Environmental Health Safety Agency)

In 2005 AFSSA/AFSSE conducted a human health risk assessment of fipronil.[18] The report concluded on the basis of modelling results for exposure scenarios compared to the most relevant toxicological reference values (i.e. acute, subacute and chronic NOELs) and on the basis of other available data, that:

- the theoretical dietary exposure of the adult population to fipronil residues remains within the set safety limits, but for young children there are cases where exposure scenarios exceed the ADI. The report emphasised that very few analyses of fipronil residues in food stuffs were available and analyses were mainly limited to uses requested within the framework of the European re-evaluation (maize and sunflower)
- the use of domestic biocidal products and plant protection products bearing the note 'approved for use in gardens' presents an acceptable risk for an adult applier (with the exception of the 'Special wasp and hornet nests' product, which should be reserved for professional use)
- exposures linked to contact with animals treated with veterinary medicinal products containing fipronil present an acceptable risk. The report noted that safety margins were lowest for young children and therefore attention should be drawn to precautionary statements on domestic products addressing a possible risk to young children
- due to lack of available exposure data for farmers and pest control professionals, potential risk could not be evaluated.

## 3.5 Summary of public submissions

In addition to specific studies provided by registrants and approval holders, submissions were received from the public in relation to the announcement of the review of fipronil.

- The horticulture industry provided a consolidated response. Fipronil has a significant role in pest management strategies in brassicas, bananas, mushrooms, potatoes and the nursery industry, including its use as a rotational option in pests prone to developing resistance to chemicals.
- The Queensland Fruit and Vegetable Growers expressed concern that the concerns associated with the veterinary uses of fipronil should not prejudice agricultural uses. The organisation has not been notified by its growers of adverse reactions to the use of fipronil in horticultural crops and it is important for its growers to maintain access to fipronil.

[18] AFSSA/AFSSE 2005, *Assessment of the risks to human health from exposure to fipronil*. March 2005

- The Australian Plague Locust Commission advised that fipronil is an important pesticide for the control of locust and grasshopper pest species in Australia. Fipronil has occupational health and safety benefits for staff when compared with the organophosphorus pesticides traditionally used for locust control. It can also be used at low field doses.
- A member of the Professional Pest Management Industry advised that they have had excellent results with fipronil-based products, with no worker health and safety issues. The member is also not aware of any such issues within the industry.
- The National Toxics Network expressed concern about the continued use of fipronil, based on human and mammalian toxicity and effects on the environment.
- A dog breeder advised that they have used Frontline spray and spot-ons on their dogs for more than eight years with no adverse effects. The products have been used on greyhounds, whippets and Australian terriers.

# 4 PROPOSED REVIEW FINDINGS

On the basis of the evaluation of the submitted data and information, the following recommendations are made with regard to the continued approval of the active constituent fipronil, registration of fipronil products and label approvals in Australia.

## 4.1 Affirm approvals of the active constituent

The APVMA is satisfied that, provided the conditions to which an approval is currently subject are complied with, the continued use of, or any other dealings with, the active constituent fipronil would not be likely to have an effect that is harmful to human beings or animals. The APVMA recommends that active constituent approval listed in Appendix A be affirmed.

## 4.2 Affirm conditions of label approval

The APVMA is satisfied that for three fipronil formulations (HG BA 0.5 g/kg or less in plastic labyrinth, BA 3.4 g/kg or less in propylene glycol impregnated in cardboard and LD 50 g/L or less), the most recently approved labels of the associated products in Appendix A contain adequate instructions in relation to the criteria set out in 14(3)(g) of the Agvet Codes as well as those referred to in Regulations 11 and 12 of the Agvet Code Regulations. The relevant products and approved labels are:

| Product number | Product name | Registrant | Label approval number |
|---|---|---|---|
| 49646 | Goliath Cockroach Bait | BASF Australia Ltd | 0403 |
| 58478 | Amulet Cue Lure Fruit Fly Stations | BASF Australia Ltd | 1205 |
| 60664 | Crop Care Amulet Cue-Lure Fruit Fly Stations | Crop Care Australasia Pty Ltd | 0408 |
| 63004 | Wolsit T-35 | Dr Wolman GMBH | 0510 |

Note that two of these formulations (BA 3.4 g/kg or less in propylene glycol impregnated in cardboard and LD 50 g/L or less) were added to the FAISD Handbook after the commencement of the review. These two formulations and associated products have not been included in the full review process and have only been considered in terms of sensitisation and the necessity for the 180 statement.

## 4.3 Vary conditions of label approval

For the labels of products in Appendix A (other than those listed in the table in Section 4.2), the APVMA is not satisfied that they contain adequate instructions in relation to the criteria set out in 14(3)(g) of the Agvet Codes as well as those referred to in Regulations 11 and 12 of the Agvet Code Regulations. However, the APVMA is satisfied that the conditions of label approval for these products can be varied in such a way that they do contain adequate instructions in accordance with section 14(3)(g) of the Agvet Codes.

Specific variations to labels involve the following changes:

- For agricultural and veterinary products, amend the first aid instructions in accordance with the recommendations of the review (see Section 4.3.1, below).
- For agricultural and veterinary products, amend the safety directions in accordance with the recommendations of the review (see Section 4.3.2, below).
- For agricultural products and veterinary spray products, amend or include new re-entry intervals and/or rehandling periods in accordance with the recommendations of the review (see Section 4.3.3, below).
- For veterinary spray and spot-on products, delete the following human safety warning in accordance with the recommendations of the OCSEH:

  > 'Do not use [Product Name] if you or your pet have a known hypersensitivity to insecticides or alcohol.'

- For veterinary spray and spot-on products, include animal safety warnings in accordance with the recommendations of the review (see Section 4.3.4, below).

### 4.3.1 First aid instructions

First aid instruction 'a' is to appear on the labels of all products containing fipronil, except for products containing both fipronil and thiodicarb:

> 'If poisoning occurs, contact a doctor or Poisons Information Centre.
> Phone Australia 131126; New Zealand 0800 764 766.'

First aid instruction 'm' is to appear on the labels of products containing both fipronil and thiodicarb:

> 'If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre Phone, e.g. Australia 131 126; New Zealand 0800 764 766 or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.'

### 4.3.2 Safety directions and personal protective equipment (PPE)

The recommended safety directions for the reviewed fipronil products are summarised in the tables below.

#### ENTRIES WITH NO CHANGE

| FORMULATION |
|---|
| HG BA 0.5 g/kg or less in plastic labyrinth |
| BA 3.4 g/kg or less in propylene glycol impregnated in cardboard * |
| GR 1 g/kg or less |
| LD 50 g/L or less * |

** These entries have only been evaluated in terms of sensitisation and the necessity for the 180 statement. The remaining safety directions were not reviewed in either the toxicology or OHS reports as the entry occurred after the data-call in period for the Fipronil Review.*

## NEW ENTRIES

| BA GEL 0.5 g/kg OR LESS | |
|---|---|
| 351 | Wash hands after use |

*Note: This entry replaces HG BA gel 0.5 g/kg or less*

| BRODIFACOUM HG BA GRANULAR 0.05 g/kg OR LESS | |
|---|---|
| 130 133 | Poisonous if swallowed. |
| 160 162 | May irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 340 342 | If product on skin, immediately wash area with soap and water. |
| 351 | Wash hands after use. |
| 400 | Vitamin K1 (Phytomenadione) is antidotal. |

*Note: This is a new entry for baits containing brodifacoum 0.5 g/kg or less with fipronil 0.04 g/kg or less. The safety directions were not reviewed in either the toxicology or OHS reports. As the entry is occurring after the commencement of the review, ONLY the 180 statement has been considered.*

## AMENDED ENTRIES

| SC 100 g/L OR LESS | |
|---|---|
| 129 133 | Harmful if swallowed. |
| 160 162 | May irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 351 | Wash hands after use. |
| 279 280 281 290 291b 298a 295 | When opening the container and preparing spray wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, chemical resistant footwear, and elbow-length PVC or nitrile gloves. |
| 279 282 290 292b 295 | When using the prepared spray wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295, 298a, 300 303 | If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge. |
| 360 361 364 365 366 | After each day's use, wash gloves, respirator, and if rubber wash with detergent and warm water, and contaminated clothing. |

| SC 200 g/L OR LESS, MORE THAN 100 g/L | |
|---|---|
| 129 132 133 | Harmful if inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 279 280 281 290 291b 299 298a 295 | When opening the container and preparing spray wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, face shield or goggles, chemical resistant footwear, and elbow-length PVC or nitrile gloves. |
| 279 282 290 292b 295 | When using the prepared spray wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295 298a 300 303 | If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge. |
| 351 | Wash hands after use. |
| 360 361 364 365 366 | After each day's use, wash gloves, respirator, and if rubber wash with detergent and warm water, face shield or goggles and contaminated clothing. |

| SC 500 g/L OR LESS, MORE THAN 200 g/L | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |
| 161 164 | Will irritate the skin. |
| 210 164 | Avoid contact with the skin. |
| 279 280 281 290 291b 300 303 295 | When opening the container and preparing slurry wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, chemical resistant footwear and elbow-length PVC or nitrile gloves. |
| 279 282 290 292b 295 306 | When using the prepared slurry wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves and a disposable dust mask. |
| 351 | Wash hands after use. |
| 360 361 366 | After each day's use, wash gloves and contaminated clothing. |

| WG 800 g/kg OR LESS | |
|---|---|
| 130 131 132 133 | Poisonous if absorbed by skin contact, inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 220 221 | Do not inhale dust. |
| 279 280 281 290 292b 295 299 | When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow length PVC or nitrile gloves and face shield or goggles. |
| | When using the prepared spray wear cotton overall buttoned to the neck |

| | |
|---|---|
| 279 282 290 292b 295 | and wrist or equivalent clothing and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295 298a 300 303 | If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge. |
| | If product in eyes, wash it out immediately with water. |
| 340 343 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 350 | |
| 360 361 364 365 366 | After each day's use, wash gloves, respirator, and if rubber wash with detergent and warm water, face shield or goggles and contaminated clothing. |

### UL 25 g/L OR LESS

| | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 279 280 281 290 295 | When opening the container and preparing spray wear elbow-length PVC or nitrile gloves. |
| 351 | Wash hands after use. |
| 360 361 | After each day's use wash gloves. |

### HV LD 2.5 g/L OR LESS

| | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 279 283 290 312 | When using the product wear rubber gloves. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use. |
| 360 361 | After each day's use, wash gloves. |

### HV SA 100 g/L OR LESS

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use. |

### SC 400 g/L OR LESS THIODICARB, WITH FIPRONIL 80 g/L OR LESS

| | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |
| 161 162 | Will irritate the eyes. |

| | |
|---|---|
| 210 162 | Avoid contact with eyes. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 220 222 | Do not inhale vapour. |
| 190 | Repeated minor exposure may have a cumulative poisoning effect. |
| 279 280 281 282 290 292 294 296 298 300 303 | When opening the container, preparing the spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrists and a washable hat, elbow-length PVC gloves, face shield, impervious footwear and a half-facepiece respirator with combined dust and gas cartridge. |
| 350 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 360 361 362 364 366 | After each day's use, wash gloves, face shield, respirator and if rubber wash with detergent and warm water and contaminated clothing. |

| DU 5 g/kg OR LESS WITH BENTONITE PD ALL STRENGTHS | |
|---|---|
| 160 162 163 | May irritate the eyes, nose and throat. |
| 210 162 | Avoid contact with eyes. |
| 220 221 | Do not inhale dust. |
| 279 280 283 290 292b 294c 297 306 (dust) | When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist [or equivalent clothing], elbow-length chemical-resistant gloves, goggles and disposable dust facemask covering mouth and nose. |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing. |
| 351 | Wash hands after use. |

*Note: This entry ONLY takes into consideration the 180 statement. The remaining safety directions have not been re-evaluated in this review, as this entry occurred after the commencement of this review.*

## DELETED ENTRIES

| Formulation |
|---|
| EC 300 g/L or less |
| WP 10 g/kg or less |
| HG WP 10 g/kg or less |
| GB 0.2 g/kg or less |
| HG BA gel 0.5 g/kg or less |

The current entries for fipronil EC 300 g/L or less, WP 10 g/kg or less, HG WP 10 g/kg or less, and GB 0.2 g/kg or less should be deleted, as there are no registered products in these categories. The current entry for HG BA gel 0.5 g/kg or less should be deleted, as it is included under the new entry BA gel 0.5 g/kg or less.

### 4.3.3. Re-entry/re-handling statements for fipronil products

The recommended new or amended re-entry and re-handling statements are listed below:

| CROP/SITUATION | RE-ENTRY/RE-HANDLING STATEMENT |
|---|---|
| Bananas, cotton, mushrooms, pasture, potato, sorghum and sugarcane | Do not allow entry into treated areas until spray has dried. If prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and gloves. Clothing must be laundered after each day's use. |
| Brassicas | Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.<br>Do not perform high exposure activities including hand-harvesting, irrigation, pruning, topping and/or tying mature plants in brassica for 13 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use. |
| Turf | Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.<br>Do not perform high exposure activities including handweeding and transplanting for 35 days, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use. |
| Termiticide treated areas | Do not enter treated areas until the spray has dried. |
| Seed treated with fipronil products | Treated seed should be allowed to dry before re-handling. Wear dust mask when handling treated seed. |
| Animals treated with fipronil spray formulations | Animals treated with fipronil spray formulations should not be handled till the spray has dried. If prior handling is required, workers should wear rubber gloves. |
| Precautionary statement | Human flaggers, if used in aerial spraying operations, must be protected by enclosed cabs. |

### 4.3.4. Animal safety warnings for veterinary products

The recommended animal safety warnings for the veterinary spot-on and spray products are listed below.

#### VETERINARY SPOT-ON PRODUCTS

##### *Contraindications*

'Use only on [dogs*]/[cats*]. Do not use on rabbits, as adverse effects, including death, may occur. (*Select appropriate species)

Avoid applying the product directly to broken or damaged skin.

Some animals may show hair loss, skin reddening or itchiness at or around the site of application. Contact a veterinarian if you have any concerns.'

VETERINARY SPRAY PRODUCTS

*Contraindications*

'Use only on dogs and cats. Do not use on rabbits, as adverse effects, including death, may occur.

Avoid spraying the product directly onto broken or damaged skin.

Avoid placing treated animals in enclosed spaces until the spray has dried.'

## 4.4 Affirm product registrations

The variations to label instructions as outlined in Section 4.3 would satisfy the requirements for continued registration of products identified in Appendix A and the APVMA recommends that product registrations be affirmed.

## 4.5 Cancellation of all but the most recently approved label

The APVMA proposes to find that it is NOT SATISFIED that previously-approved product labels for currently registered products listed in Appendix A contain adequate instructions in relation to the criteria set out in s.14(3)(g) of the Agvet Codes. As such the approvals of these labels are recommended for cancellation.

## 4.6 Withdrawn fipronil products

A number of fipronil products (outlined in Appendix A) have been voluntarily withdrawn since the commencement of the review. Once cancellation of registration is formally effected, reconsideration is no longer required.

## 4.7 Amendments to standards

Arising from the OCSEH assessment of data submitted to the review of fipronil and the consideration of the expanded toxicological database, the OCSEH has made a number of recommendations in relation to public health standards for fipronil, which are summarised in Section 4.8.

## 4.8 Public health standards

### 4.8.1 Impurity Limits

An integral part of the safety assessment of an active constituent is a consideration of the chemical composition of the material. Active constituents will contain measurable levels of impurities, which can arise during manufacture and/or from subsequent degradation during storage. The chemical identity of these impurities is generally well characterised. The impurities present in the active constituent are usually of no particular concern since health standards are established on the basis of toxicology studies conducted using the mixture. However, for those which have high acute toxicity, genotoxicity or teratogenic potential, concentration limits need to be set, so that the toxicological profile of the active constituent does not appreciably alter in the event of slight changes in the proportions of the impurities.

In the *APVMA Standards – Active Constituents*, the composition of fipronil is listed as 950 g/kg (on a dry weight basis). No impurity limits are stated. This review did not identify any impurities of toxicological concern, therefore this standard remains appropriate.

### 4.8.2 Residue definition

In the *APVMA Standard for Maximum Residue Limits in Food and Animal Feedstuff* (APVMA, March 2011, Table 3), the residue of fipronil is defined as the sum of:

- fipronil; and
- the sulfenyl metabolite (5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl) sulfenyl]-1H-pyrazole-3-carbonitrile); and
- the sulfonyl metabolite (5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile); and
- the trifluoromethyl metabolite (5-amino-4-trifluoromethyl-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile).

In the current review, these metabolites are also referred to as MB 45950 (fipronil sulfide), MB 46136 (fipronil sulfone) and MB 46513 (desulfinyl fipronil) respectively (see Appendix VII in Volume 2 for structures and alternative nomenclature). Desulfinyl fipronil is a photodegradative product of fipronil found in plants, but is not a metabolite in mammals. Overall, it has a similar toxicity profile to fipronil. The toxicity of the mammalian metabolites fipronil sulfone and fipronil sulfide is similar to the parent compound. Therefore, from a toxicological perspective, the residue definition is appropriate.

### 4.8.3 Acceptable daily intake (ADI)

The ADI for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to

humans, intraspecies variation, the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The current Australian ADI for fipronil is 0.0002 mg/kg bw/day. It was set in June 1994 by the application of a safety factor of 100 to the NOEL of 0.02 mg/kg bw/day in a chronic/carcinogenicity rat study, based on the occurrence of neurological signs and haematological changes. This review affirmed this ADI. This is a group value to cover the parent compound and metabolites as specified by the residue definition.

### 4.8.4 Acute reference dose (ARfD)

The ARfD is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram bodyweight basis, which can be ingested over a short period of time, usually one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

The current ARfD is 0.02 mg/kg bw, based on a NOEL of 2.5 mg/kg bw for decreased landing footsplay in an acute oral neurotoxicity study in rats, incorporating a safety factor of 100. This value was established in 2006 and is a group value to cover the parent compound and metabolites as specified in the residue definition. The ARfD was previously 0.003 mg/kg bw based on the NOEL from a three-month neurotoxicity study in rats.

### 4.8.5 Drinking water quality guidelines

Health values are intended for use by health authorities in managing the health risks associated with inadvertent exposure such as a spill or misuse of a pesticide. The values are derived so as to limit intake from water alone to about 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult weighing 70 kg at a daily water consumption of 2 L over a lifetime. There is currently no guideline or health value for fipronil in Australian drinking water. Given that the ADI for fipronil is 0.0002 mg/kg bw/day, the health-based guideline value may be calculated as:

$$0.0007 \text{ mg/L} = \frac{0.02 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L/day} \times 100}$$

where:

- 0.02 mg/kg bw/day is the NOEL based on a two-year chronic study in rats.
- 70 kg is taken as the average weight of an adult.
- 0.1 is a proportionality factor based on the conservative assumption that at least 10% of the ADI will arise from the consumption of drinking water.
- 2 L/day is the estimated amount (maximum) of water consumed by an adult.
- 100 is a safety factor for using a NOEL from a study conducted in rats. The safety factor of 100 is comparable to that used for the ADI (10 for interspecies variations, 10 for intraspecies variations).

It is noted that the draft revised Australian Drinking Water Guidelines (2009) propose a guideline health value for fipronil of 0.0007 mg/L.

### 4.8.6 Poisons scheduling

Fipronil is listed in Schedule 6 of the Standard for Uniform Scheduling of Medicines and Poisons (SUSMP), except when included in Schedule 5 (preparations containing 10 per cent or less of fipronil), or in preparations containing 0.05 per cent or less of fipronil, which are unscheduled. As no new information provided for this review indicates that these levels are inappropriate, it is recommended that the current scheduling of fipronil is maintained.

### 4.8.7 First-aid Instructions

First aid instructions are substance-specific and generally apply to all formulations in which that substance is an ingredient and in concentrations at which the substance is scheduled in the SUSMP.

This review confirmed that first aid instruction 'a' remains appropriate for products containing fipronil, except for products containing both fipronil and thiodicarb.

First aid instruction 'a' appears in the *First Aid Instruction and Safety Directions (FAISD) Handbook* as follows:

> 'If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.'

For products containing both fipronil and thiodicarb, first aid instructions 'a' and 'h' should be replaced by first aid instruction 'm', as first aid instruction 'm' is appropriate for the second active constituent, thiodicarb, which is a cholinesterase-inhibiting compound. First aid instruction 'h' has been discontinued in the FAISD Handbook.

First aid instruction 'm' appears in the FAISD Handbook as follows:

> 'If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre Phone e.g. Australia 131 126; New Zealand 0800 764 766 or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.'

### 4.8.8 Safety directions

Safety directions are product-specific and apply regardless of scheduling considerations related to the product. Whilst a single entry in the safety directions section of the FAISD Handbook may cover a number of individual products, these directions apply only to that specific formulation description.

The existing safety directions and the changes recommended as an outcome of this review are detailed below.

#### EXISTING SAFETY DIRECTIONS FOR FIPRONIL

Existing safety directions for fipronil as they appear in the First Aid Instruction and Safety Directions (FAISD) Handbook are as follows:

(as listed in FAISD Handbook Edition 1/2011 current to 3 March 2011)

| BA 3.4 g/kg OR LESS IN PROPYLENE GLYCOL IMPREGNATED IN CARDBOARD (ADDED TO FAISD HANDBOOK FOLLOWING THE COMMENCEMENT OF THE REVIEW, THEREFORE NOT INCLUDED IN THE FULL REVIEW PROCESS) | |
|---|---|
| 160 162 164 | May irritate eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 351 | Wash hands after use. |
| 279 283 290 312 | When using the product wear rubber gloves. |
| 360 361 | After each day's use wash gloves. |

| DU 5 g/kg OR LESS WITH BENTONITE PD ALL STRENGTHS (ADDED TO FAISD HANDBOOK FOLLOWING THE COMMENCEMENT OF THE REVIEW, THEREFORE NOT INCLUDED IN THE FULL REVIEW PROCESS) | |
|---|---|
| 160 162 163 | May irritate the eyes, nose and throat. |
| 180 | Repeated exposure may cause allergic disorders. |
| 210 162 | Avoid contact with eyes. |
| 220 221 | Do not inhale dust. |
| 279 280 283 290 292b 294c 297 306 (dust) | When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist [or equivalent clothing], elbow-length chemical-resistant gloves, goggles and disposable dust face mask covering mouth and nose. |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing. |
| 351 | Wash hands after use. |

| EC 300 g/L OR LESS | |
|---|---|
| 129 131 133 | Harmful if absorbed by skin contact or swallowed. |
| 207 162 | Will damage eyes. |
| 160 164 | May irritate the skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 279 280 281 282 290 292b 294 297 | When opening the container, preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) elbow-length PVC gloves and goggles. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use. |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing. |

| GB 0.2 g/kg OR LESS (ADDED TO FAISD HANDBOOK FOLLOWING THE COMMENCEMENT OF THE REVIEW, THEREFORE NOT INCLUDED IN THE FULL REVIEW PROCESS) | |
|---|---|
| 180 | Repeated exposure may cause allergic disorders. |

| | |
|---|---|
| 351 | Wash hands after use. |
| 289 290 292b 294<br>360 361 366 | If applying by hand wear cotton overalls buttoned to the neck and wrist [or equivalent clothing] and elbow-length PVC gloves.<br>After each day's use, wash gloves and contaminated clothing. |

### GR 1 g/kg OR LESS

| | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 351 | Wash hands after use. |

### HG BA GEL 0.5 g/kg OR LESS

| | |
|---|---|
| 160 162 164 | May irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 351 | Wash hands after use. |

### HG BA 0.5 g/kg OR LESS IN PLASTIC LABYRINTH

Nil

### HG WP 10 g/kg OR LESS

Nil

### HV LD 2.5 g/L OR LESS

| | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 180 | Repeated exposure may cause allergic disorders. |
| 210 162 | Avoid contact with eyes. |
| 279 283 290 312 | When using the product wear rubber gloves. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 360 | Wash hands after use. |
| 361 | After each day's use, wash gloves. |

### HV SA 100 g/L OR LESS

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin. |
| 180 | Repeated exposure may cause allergic disorders. |
| 210 211 | Avoid contact with eyes and skin. |

| | |
|---|---|
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use. |

| LD 50 g/L OR LESS (ADDED TO FAISD HANDBOOK FOLLOWING THE COMMENCEMENT OF THE REVIEW AND THEREFORE NOT INCLUDED IN THE FULL REVIEW PROCESS) | |
|---|---|
| 129 133 | Harmful if swallowed |
| 210 164 | Avoid contact with skin. |
| 160 162 164 | May irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 279 280 285 283 290 294c | When opening the container, preparing product for use and using the product, wear elbow-length chemical resistant gloves. |
| 351 | Wash hands after use. |

| SC 100 g/L OR LESS | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin. |
| 180 | Repeated exposure may cause allergic disorders. |
| 210 211 | Avoid contact with eyes and skin. |
| 351 | Wash hands after use. |
| 279 280 281 282 290 291b 300 303 295 | When opening the container, preparing spray and using the prepared spray, wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, half facepiece respirator with combined dust and gas cartridge, and elbow-length PVC or nitrile gloves. |
| 360 361 366 364 | After each day's use, wash gloves and contaminated clothing and respirator, and if rubber wash with detergent and warm water. |

| SC 200 g/L OR LESS, MORE THAN 100 g/L | |
|---|---|
| 129 132 133 | Harmful if inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 180 | Repeated exposure may cause allergic disorders. |
| 210 211 | Avoid contact with eyes and skin. |
| 279 280 285 290 292b 294 297 | When opening the container and preparing the product for use wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC gloves and goggles. |
| 279 282 290 292b 294 | When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves. |
| 351 | Wash hands after use. |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing. |

| SC 500 g/L OR LESS, MORE THAN 200 g/L | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |
| 210 164 | Avoid contact with skin. |
| 279 280 285 282 290 292b 294 | When opening the container, preparing product for use, and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves. |
| 351 | Wash hands after use. |
| 360 361 366 | After each day's use, wash gloves and contaminated clothing. |

| UL 25 g/L OR LESS | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 279 280 281 290 294 | When opening the container and preparing spray wear elbow-length PVC gloves. |
| 351 | Wash hands after use. |
| 360 361 | After each day's use, wash gloves. |

| WG 800 g/kg OR LESS | |
|---|---|
| 130 131 132 133 | Poisonous if absorbed by skin contact, inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 220 221 | Do not inhale dust. |
| 279 280 285 282 290 292b 294 299 | When opening the container, preparing product for use, and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC gloves and face shield or goggles. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 350 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 360 361 365 366 | After each day's use, wash gloves, face shield or goggles and contaminated clothing. |

| WP 10 g/kg OR LESS | |
|---|---|
| 279 280 285 290 294b | When opening the container and preparing product for use wear elbow-length rubber gloves. |
| 360 361 | After each day's use, wash gloves. |

| SC 400 g/L OR LESS THIODICARB, WITH FIPRONIL 80 g/L OR LESS | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |

| | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 190 | Repeated minor exposure may have a cumulative poisoning effect. |
| 210 211 | Avoid contact with eyes and skin. |
| 220 222 | Do not inhale vapour. |
| 279 280 281 282 290 292 294 296 298 300 303 | When opening the container, preparing spray and using the prepared spray wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length PVC gloves, face shield, impervious footwear and half facepiece respirator with combined dust and gas cartridge. |
| 350 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 360 361 362 364 366 | After each day's use, wash gloves, face shield, respirator and if rubber wash with detergent and warm water, and contaminated clothing. |

### 4.8.8.2 RECOMMENDED SAFETY DIRECTIONS FOR FIPRONIL

This review recommends changes to the safety directions for some agricultural and veterinary chemical products. The recommended safety directions are summarised below.

#### ENTRIES WITH NO CHANGE

| FORMULATION |
|---|
| HG BA 0.5 g/kg or less in plastic labyrinth |
| BA 3.4 g/kg or less in propylene glycol impregnated in cardboard * |
| GR 1 g/kg or less |
| LD 50 g/L or less * |

** These entries have only been evaluated in terms of sensitisation and the necessity for the 180 statement. The remaining safety directions were not reviewed in either the toxicology or OHS reports as the entry occurred after the data-call in period for the Fipronil Review.*

#### NEW ENTRIES

| BA GEL 0.5 g/kg OR LESS | |
|---|---|
| 351 | Wash hands after use |

*Note: This entry replaces HG BA gel 0.5 g/kg or less*

| BRODIFACOUM HG BA GRANULAR 0.05 g/kg OR LESS | |
|---|---|
| 130 133 | Poisonous if swallowed. |
| 160 162 | May irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 340 342 | If product on skin, immediately wash area with soap and water. |

| | |
|---|---|
| 351 | Wash hands after use. |
| 400 | Vitamin K1 (Phytomenadione) is antidotal. |

*Note: This is a new entry for baits containing brodifacoum 0.5 g/kg or less with fipronil 0.04 g/kg or less. The safety direc tions were not reviewed in either the toxicology or OHS reports. As the entry is occurring after the commencement of the review, ONLY the 180 statement has been considered.*

## AMENDED ENTRIES

### SC 100 g/L OR LESS

| | |
|---|---|
| 129 133 | Harmful if swallowed. |
| 160 162 | May irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 351 | Wash hands after use. |
| 279 280 281 290 291b 298a 295 | When opening the container and preparing spray wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, chemical resistant footwear, and elbow-length PVC or nitrile gloves. |
| 279 282 290 292b 295 | When using the prepared spray wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295 298a 300 303 | If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge. |
| 360 361 364 365 366 | After each day's use wash gloves, respirator, and if rubber wash with detergent and warm water, and contaminated clothing. |

| SC 200 g/L OR LESS, MORE THAN 100 g/L | |
|---|---|
| 129 132 133 | Harmful if inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 340 343 | If product in eyes wash it out immediately with water. |
| 279 280 281 290 291b 299 298a 295<br>279 282 290 292b 295 | When opening the container and preparing spray wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, face shield or goggles, chemical resistant footwear, and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295 298a 300 303 | When using the prepared spray wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge. |
| 351 | Wash hands after use. |
| 360 361 364 365 366 | After each day's use wash gloves, respirator, and if rubber wash with detergent and warm water, face shield or goggles and contaminated clothing. |

| SC 500 g/L OR LESS, MORE THAN 200 g/L | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |
| 161 164 | Will irritate the skin. |
| 210 164 | Avoid contact with the skin. |
| 279 280 281 290 291b 300 303 295 | When opening the container and preparing slurry wear chemical resistant clothing buttoned to the neck and wrist and a washable hat, chemical resistant footwear and elbow-length PVC or nitrile gloves. |
| 279 282 290 292b 295 306 | When using the prepared slurry wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves and a disposable dust mask. |
| 351 | Wash hands after use. |
| 360 361 366 | After each day's use, wash gloves and contaminated clothing |

| WG 800 g/kg OR LESS | |
|---|---|
| 130 131 132 133 | Poisonous if absorbed by skin contact, inhaled or swallowed. |
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 220 221 | Do not inhale dust. |
| 279 280 281 290 292b 295 299 | When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow length PVC or nitrile gloves and face shield or goggles. |
| 279 282 290 292b 295 | When using the prepared spray wear cotton overall buttoned to the neck and wrist or equivalent clothing and elbow-length PVC or nitrile gloves. |
| 289 290 291b 295, 298a, 300 303 | If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length PVC or nitrile gloves, chemical resistant footwear and half facepiece respirator with combined dust and gas cartridge |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 350 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 360 361 364 365 366 | After each day's use, wash gloves, respirator, and if rubber wash with detergent and warm water, face shield or goggles and contaminated clothing |

| UL 25 g/L OR LESS | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 279 280 281 290 295 | When opening the container and preparing spray wear elbow-length PVC or nitrile gloves. |
| 351 | Wash hands after use. |
| 360 361 | After each day's use wash gloves |

| HV LD 2.5 G/L OR LESS | |
|---|---|
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 279 283 290 312 | When using the product wear rubber gloves. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use. |
| 360 361 | After each day's use, wash gloves. |

| HV SA 100 g/L OR LESS | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin. |
| 210 211 | Avoid contact with eyes and skin. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 351 | Wash hands after use |

| SC 400 g/L OR LESS THIODICARB, WITH FIPRONIL 80 g/L OR LESS | |
|---|---|
| 130 132 133 | Poisonous if inhaled or swallowed. |
| 161 162 | Will irritate the eyes. |
| 210 162 | Avoid contact with eyes. |
| 340 343 | If product in eyes, wash it out immediately with water. |
| 220 222 | Do not inhale vapour. |
| 190 | Repeated minor exposure may have a cumulative poisoning effect. |
| 279 280 281 282 290 292 294 296 298 300 303 | When opening the container, preparing the spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrists and a washable hat, elbow-length PVC gloves, face shield, impervious footwear and a half-facepiece respirator with combined dust and gas cartridge. |
| 350 | After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. |
| 360 361 362 364 366 | After each day's use, wash gloves, face shield, respirator and if rubber wash with detergent and warm water and contaminated clothing. |

| DU 5 g/kg OR LESS WITH BENTONITE PD ALL STRENGTHS | |
|---|---|
| 160 162 163 | May irritate the eyes, nose and throat. |
| 210 162 | Avoid contact with eyes. |
| 220 221 | Do not inhale dust. |
| 279 280 283 290 292b 294c 297 306 (dust) | When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist [or equivalent clothing], elbow-length chemical-resistant gloves, goggles, and disposable dust face mask covering mouth and nose. |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing. |
| 351 | Wash hands after use. |

*Note: This entry ONLY takes into consideration the 180 statement. The remaining safety directions have not been re-evaluated in this review, as this entry occurred after the commencement of this review.*

## DELETED ENTRIES

| FORMULATION |
| --- |
| EC 300 g/L or less |
| WP 10 g/kg or less |
| HG WP 10 g/kg or less |
| GB 0.2 g/kg or less |
| HG BA gel 0.5 g/kg or less |

The current entries for fipronil EC 300 g/L or less, WP 10 g/kg or less, HG WP 10 g/kg or less and GB 0.2 g/kg or less should be deleted, as there are no registered products in these categories. The current entry for HG BA gel 0.5 g/kg or less should be deleted, as it is included under the new entry BA gel 0.5 g/kg or less.

# APPENDICES

# APPENDIX A – ACTIVE CONSTITUENTS AND PRODUCTS

### Table A1:Active constituent approvals included in the review

| Approval number | Active constituent name | Registrant |
|---|---|---|
| 46789 | Fipronil | BASF Australia Ltd |
| 49120 | Fipronil Manufacturing Concentrate | BASF Australia Ltd |
| 51985 | Fipronil | BASF Australia Ltd |
| 52547 | Fipronil Manufacturing Concentrate | BASF Australia Ltd |

### Table A2: Veterinary products included in the review

| Product number | Product name | Registrant | Label approval number |
|---|---|---|---|
| 46828 | Frontline Spray | Merial Australia Pty Ltd | 46828/0102<br>46828/02<br>46828/03<br>46828/04<br>46828/0400<br>46828/0410<br>46828/0807<br>46828/0900<br>46828/1098<br>46828/2675 |
| 48523 | Frontline Top Spot Cat | Merial Australia Pty Ltd | 48523/01<br>48523/0302<br>48523/0400<br>48523/0510<br>48523/0798<br>48523/0900 |
| 48606 | Frontline Top Spot Small Dog | Merial Australia Pty Ltd | 48606/01<br>48606/0798<br>48606/1098 |
| 49825 | Frontline Top Spot Medium Dog | Merial Australia Pty Ltd | 49825/01<br>49825/0798<br>49825/1098 |
| 49826 | Frontline Top Spot Large Dog | Merial Australia Pty Ltd | 49826/01<br>49826/0798<br>49826/1098 |
| 51304 | Startgard For Puppies | Merial Australia Pty Ltd | 51304/1098 |
| 51530 | Startgard For Kittens | Merial Australia Pty Ltd | 51530/1298 |
| 52043 | Frontline Top Spot Extra Large Dog | Merial Australia Pty Ltd | 52043/0699 |

| | | | |
|---|---|---|---|
| 52327 | Frontline Top Spot For Dogs | Merial Australia Pty Ltd | 52327/0302<br>52327/0610<br>52327/0807<br>52327/0900<br>52327/0999 |
| 54523 | Frontline Plus (Fipronil Plus (S)-Methoprene) For Dogs | Merial Australia Pty Ltd | 54523/0403<br>54523/0502<br>54523/0807<br>54523/0906<br>54523/1209 |
| 54524 | Frontline Plus (Fipronil Plus (S)-Methoprene) For Cats | Merial Australia Pty Ltd | 54524/0502<br>54524/0503<br>54524/0906<br>54524/1209 |
| 56123 | Startgard Plus for Puppies | Merial Australia Pty Ltd | 56123/0802 |
| 56124 | Startgard Plus for Kittens | Merial Australia Pty Ltd | 56124/0802 |

### Table A3:Agricultural products included in the review

| Product number | Product name | Registrant | Label approval number |
|---|---|---|---|
| 46793 | Regent 200SC Insecticide | BASF Australia Ltd | 46793/01<br>46793/03<br>46793/0399<br>46793/0402<br>46793/0403<br>46793/0499<br>46793/0501<br>46793/0605<br>46793/0901<br>46793/0997<br>46793/0999<br>46793/1099<br>46793/1199 |
| 47407 | Regent 800WG Insecticide | BASF Australia Ltd | 47407/0399<br>47407/0402<br>47407/0403<br>47407/0499<br>47407/0501<br>47407/0605<br>47407/0901<br>47407/0997<br>47407/1199 |
| 49434 | Cosmos Insecticidal Seed Treatment | BASF Australia Ltd | 49434/0403<br>49434/0499<br>49434/0598<br>49434/0699<br>49434/0798<br>49434/0899<br>49434/0997 |

| | | | |
|---|---|---|---|
| | | | 49434/1100<br>49434/1101<br>49434/1204 |
| 49646 | Goliath Cockroach Bait | BASF Australia Ltd | 49646/0403<br>49646/0997 |
| 49647 | Goliath Cockroach Gel | BASF Australia Ltd | 49647/0403<br>49647/0404<br>49647/0997 |
| 50285 | Adonis 8.5UL Insecticide | BASF Australia Ltd | 50285/0403<br>50285/1199 |
| 51720 | Combat Ant - Rid Relief From Tough Ant Problems Ant Baits | Henkel Australia Pty Ltd | 51720/0400<br>51720/0409<br>51720/0504<br>51720/0799<br>51720/1000 |
| 53156 | Adonis 3UL Insecticide | BASF Australia Ltd | 53156/0403<br>53156/0900 |
| 54624 | Termidor Residual Termiticide and Insecticide | BASF Australia Ltd | 54624/0204<br>54624/0403<br>54624/0806<br>54624/0808<br>54624/0809<br>54624/1002<br>54624/1004<br>54624/1007 |
| 55553 | Maxforce Gold Gel Insecticide | Bayer Cropscience Pty Ltd | 55553/0402<br>55553/0802 |
| 57764 | Impede Insecticide | BASF Australia Ltd | 57764/0503 |

### Table A4: Products registered and active constituents approved after the commencement of the review subject to the outcomes of the review

| Product number | Product name | Registrant | Label approval number |
|---|---|---|---|
| 58478 | Amulet Cue Lure Fruit Fly Stations | BASF Australia Ltd | 58478/1205 |
| 58661 | Mortein Rat Kill With Flea Eliminator | Reckitt Benckiser (Australia) Pty Limited | 58661/0208<br>58661/0309<br>58661/0606 |
| 58884 | Nufarm Impede Insecticide | Nufarm Australia Limited | 58884/0604 |
| 58885 | Nufarm Adonis 3UL Insecticide | Nufarm Australia Limited | 58885/0307<br>58885/0604<br>58885/0605<br>58885/1006 |

| | | | |
|---|---|---|---|
| 60284 | Nufarm Regent 200SC Insecticide | Nufarm Australia Limited | 60284/0406<br>60284/0809<br>60284/1005<br>60284/1208 |
| 60654 | Termidor Dust Termiticide | BASF Australia Ltd | 60654/0207<br>60654/49634 |
| 60664 | Crop Care Amulet Cue-Lure Fruit Fly Stations | Crop Care Australasia Pty Ltd | 60664/0306<br>60664/0408 |
| 60887 | Ilium Frontera Spray | Troy Laboratories Pty Ltd | 60887/0207<br>60887/1207 |
| 61345 | Crop Care Cosmos Insecticidal Seed Treatment | Crop Care Australasia Pty Ltd | 61345/1106 |
| 61632 | Nufarm Gard Insecticide | Nufarm Australia Limited | 61632/0107 |
| 61820 | Imtrade Regal 800 WG Insecticide | Imtrade Australia Pty Ltd | 61820/0309<br>61820/0909<br>61820/51738 |
| 62236 | Legion 200SC Insecticide | Crop Care Australasia Pty Ltd | 62236/0609<br>62236/0707 |
| 62372 | Nufarm Regent 800 WG Insecticide * | Nufarm Australia Limited | 62372/1207 * |
| 63004 | Wolsit T-35 | Dr Wolman GMBH | 63004/0510 |
| 63435 | Barmac Fipro Force Residual Termiticide | Barmac Industries Pty Ltd | 63435/1108 |
| 63581 | Surefire Vista 200SC Insecticide | PCT Holdings Pty Ltd | 63581/0309<br>63581/50826 |
| 63600 | Transfer Termiticide | Garrards Pty Ltd | 63600/0309 |
| 63885 | Mortein Rat Kill Throwpacks Household Protection | Reckitt Benckiser (Australia) Pty Limited | 63885/0409 |
| 63960 | Campbell Kaiser 200SC Insecticide | Colin Campbell (Chemicals) Pty Ltd | 63960/1209 |
| 64449 | Ultrathor Water Based Termiticide | Ensystex Australasia Pty Ltd | 64449/50519 |
| 65356 | AW Flack Insecticide | Agri West Pty Limited | 65356/50745<br>65356/52702 |
| 65457 | Frontline Original for Cats | Merial Australia Pty Ltd | 65457/50969 |
| 65655 | Frontline Original for Large Dogs | Merial Australia Pty Ltd | 65655/51506 |
| 65660 | Frontline Original for Medium Dogs | Merial Australia Pty Ltd | 65660/51517 |
| 65661 | Frontline Original for Small Dogs | Merial Australia Pty Ltd | 65661/51520 |

| | | | |
|---|---|---|---|
| 65663 | Frontline Original for Extra Large Dogs | Merial Australia Pty Ltd | 65663/51522 |

** Registration of Nufarm Regent 800 WG Insecticide was not renewed for the financial year 2010-2011 and accordingly this registration ended on 30 June 2010.*

| Approval number | Active constituent name | Approval Holder |
|---|---|---|
| 58418 | Fipronil | Gharda Australia Pty Ltd |
| 59286 | Fipronil | BASF Australia Ltd |
| 63161 | Fipronil | Shanghai Safe-Chem International Trade Co Limited |
| 64070 | Fipronil | Farmoz Pty Limited |
| 64725 | Fipronil | Imtrade Australia Pty Ltd |
| 65337 | Fipronil | Agrogill Chemicals Pty Ltd |
| 65338 | Fipronil | Ospray Pty Ltd |

### Table A5: Products for which registration was withdrawn since the commencement of the review

| Product number | Product name | Registrant |
|---|---|---|
| 48921 | Chipco Choice Insecticide | BASF Australia Ltd |
| 51371 | Semevin Super Seed Dressing Insecticide | BASF Australia Ltd |
| 53264 | Presto Insecticide | BASF Australia Ltd |
| 53737 | Presto 100 Insecticide | BASF Australia Ltd |
| 54587 | Goliath Gold Gel Insecticide | BASF Australia Ltd |
| 62372 | Nufarm Regent 800 WG Insecticide | Nufarm Australia Limited |

# APPENDIX B – REFERENCES

Please refer to the individual component reports for the cited references.

- For references cited in Section 3.1 Toxicology, please refer to Volume 2 – Review of the Mammalian Toxicology and Metabolism/Toxicokinetics of Fipronil.
- For references cited in Section 3.2 Occupational health and safety, please refer to Volume 2 – Occupational Health and Safety Assessment of Fipronil.
- For references cited in Section 3.3.1 Animal Safety – Literature Review, please refer to Volume 2 – Safety of Fipronil in Dogs and Cats: A Review of Literature.
- For references cited in Section 3.3.2 Animal Safety – Animal Safety Studies, please refer to Volume 2 – Review of Animal Safety Studies for Fipronil in the Dog and Cat.

# ACRONYMS AND ABBREVIATIONS

### LENGTH

| | |
|---|---|
| cm | centimetre |
| m | metre |
| µm | micrometre |
| mm | millimetre |

### WEIGHT

| | |
|---|---|
| kg | kilogram |
| g | gram |
| µg | microgram |
| mg | milligram |
| wt | weight |
| bw | bodyweight |

### DOSING

| | |
|---|---|
| mg/kg bw/day | mg/kg bodyweight/day |

### VOLUME

| | |
|---|---|
| L | litre |
| mL | millilitre |

### OTHER

| | |
|---|---|
| hPa | hectoPascals |

### CONCENTRATION

| | |
|---|---|
| ppm | parts per million |
| nM | nanomoles |

### CLINICAL CHEMISTRY, HAEMATOLOGY AND ORGANISATIONS

| | |
|---|---|
| ADE | Adverse drug experience |
| ADI | Acceptable daily intake |
| AERP | Adverse Experience Reporting Program (through APVMA) |
| AFSSA | Agence Française de Sécurité Sanitaire des Aliments (French Food Health Safety Agency) |
| AFSSE | Agence Française de Sécurité Sanitaire Environmentale (French Environmental Health Safety Agency) |
| ai | active ingredient |
| ALP | alkaline phosphatase |
| APVMA | Australian Pesticides and Veterinary Medicines Authority |
| ARfD | Acute Reference Dose |
| $C_{max}$ | Maximum plasma drug concentration |
| DFR | dislodgeable foliar residue |
| EC | emulsifiable concentrate |

| | |
|---|---|
| EBOB | 4’-ethynyl-4-n-[2,3-3H2] propylbicycloorthobenzoate |
| FAI | First aid instructions |
| FAISD | First aid instruction and safety directions |
| GABA | gamma-aminobutyric acid |
| Hb | Haemoglobin |
| Hct | Haematocrit |
| HV/HG | home veterinary/home garden |
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| $K_m$ | Michaelis-Menten constant |
| LC50 | median lethal concentration |
| LD50 | median lethal dose |
| LOEL | Lowest Observed Effect Level |
| MOE | Margin of exposure |
| NOEL | No Observed Effect Level |
| NOAEL | No Observed Adverse Effect Level |
| MRL | Maximum Residue Limit |
| NRS | National Registration Scheme |
| OCSEH | Office of Chemical Safety and Environmental Health |
| OHS | occupational health and safety |
| PHED | Pesticide Handlers Exposure Database |
| PTU | propylthiouracil |
| SC | suspension concentrate |
| SD | Safety directions |
| SUSMP | Standard for the Uniform Scheduling of Medicines and Poisons |
| T3 | Triiodothyroxine |
| T4 | Thyroxine |
| TBPS | tert-butylbicyclo-phosphoro-thionate |
| TSH | Thyroid stimulating hormone |

| | |
|---|---|
| US EPA | United States Environmental Protection Agency |
| ULV | Ultra-low volume |
| VIN | Veterinary Information Network |
| $V_{max}$ | Maximal rate of enzyme reaction at saturating substrate concentration |