



Australian Pesticides &
Veterinary Medicines Authority

The Reconsideration of Approvals and Registrations Relating to FIPRONIL

REVIEW SCOPE DOCUMENT

September 2003

**Australian Pesticides &
Veterinary Medicines Authority**

**Canberra
Australia**

ã National Registration Authority for Agricultural and Veterinary Chemicals

This work is copyright. Apart from any use permitted under the *Copyright Act 1968*, no part may be reproduced without permission from the National Registration Authority for Agricultural and Veterinary Chemicals.

This scope document for the review of FIPRONIL is published by the Australian Pesticides & Veterinary Medicines Authority (APVMA). For further information about this review or the Veterinary Medicines Review Program contact:

Manager, Veterinary Medicines Review
Australian Pesticides & Veterinary Medicines Authority
PO Box E240
Kingston ACT 2604
Australia

Telephone: 61 2 6272 3213
Facsimile 61 2 6272 3218
Email: chemrev@apvma.gov.au
APVMA web site: <http://www.apvma.gov.au>

INDEX

INDEX	3
FOREWORD	4
SUMMARY.....	4
1. INTRODUCTION	5
2. REGULATORY STATUS AND USE PATTERNS OF FIPRONIL IN AUSTRALIA.....	5
3. REASONS FOR THE RECONSIDERATION OF APPROVALS AND REGISTRATIONS RELATING TO FIPRONIL	6
4. SCOPE OF THE REVIEW	6
5. SUSPECTED ADVERSE EXPERIENCE REPORTS	7
6. TOXICOLOGICAL ISSUES	10
7. OCCUPATIONAL HEALTH AND SAFETY ISSUES	10
8. ANIMAL SAFETY ISSUES	10
9. INTERNATIONAL REGULATORY STATUS OF FIPRONIL	11
10. SUBMISSIONS FROM THE PUBLIC INVITED	11
11. DATA ASSESSMENT AND POSSIBLE OUTCOMES	11
12. CONSULTATION THROUGHOUT THE REVIEW PROCESS	12

Review Scope Document (FIPRONIL)

FOREWORD

The Australian Pesticides & Veterinary Medicines Authority (APVMA) is the National Registration Authority for Agricultural and Veterinary Chemicals. When reading this document, "APVMA" means "NRA".

SUMMARY

The APVMA has initiated the reconsideration of the approvals of the active constituent fipronil, registration of products containing fipronil and the approval of all associated labels. This document defines the scope of the matters of concern to the APVMA and outlines the kinds of information the APVMA will use to conduct a comprehensive scientific assessment of fipronil.

Fipronil is a broad spectrum insecticide that belongs to a relatively new class of pesticides. Its mechanism of action is interference with the insect central nervous system. Fipronil is used in veterinary chemical products to control fleas and ticks on cats and dogs and in agricultural chemical products to control a range of insect pests in agricultural crops. It is also included in a number of household products such as cockroach baits and gels and in ant bait stations.

The APVMA has received a number of human and animal adverse experience reports involving products containing fipronil. Reports include 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.

As a result of these reports the APVMA will consider whether fipronil and products containing fipronil in the context of both agricultural and veterinary uses:

- may be an undue hazard to the safety of people exposed to it during its handling;
- may have an effect that is harmful to human beings;
- may have an unintended effect that is harmful to animals; and whether
- product labels contain adequate instructions with regard to the safe handling of the product or other warning and precautionary instructions.

The APVMA will review the following matters relevant to active constituent approvals, product registrations and label approvals for fipronil:

- toxicity of fipronil primarily in relation to dermal irritation and the induction of skin sensitisation;
- 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; risk to workers on re-entry to treated areas or humans handling animals after they have been treated;
- animal safety; and

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

The reconsideration will be finalised after the APVMA has reviewed all the data and other information provided to it for this purpose.

1. INTRODUCTION

Section 31 of the Agvet Codes authorises the APVMA to reconsider:

- (a) the approval of an active constituent for a proposed or existing chemical product;
- (b) the registration of a chemical product; and
- (c) the approval of a label for containers for a chemical product.

The APVMA has decided to reconsider the approvals of the active constituent fipronil, the registrations of products containing fipronil and approvals of associated labels because there have been a number of reports of adverse effects in humans and in animals. These adverse experience reports have raised concerns about the use and safety in use of fipronil and products containing fipronil. Details of active approvals and product registrations subject to reconsideration are provided in Appendix 1.

2. REGULATORY STATUS AND USE PATTERNS OF FIPRONIL IN AUSTRALIA

2.1 Active constituents and products

At the commencement of the review, there were 4 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. It should be noted that any active constituent approvals and product registrations that occur after the commencement of the review would be made subject to the outcomes of the review.

Fipronil is a broad-spectrum insecticide that belongs to a relatively new class of pesticides. Fipronil was first used in Australia as an agricultural chemical product in 1994. It is now widely used in agriculture as a seed dressing and for the control of locusts and a wide range of other insect pests in pasture, agricultural crops and domestic and commercial turf. Fipronil is also included in a number of household products and commercial building treatments such as cockroach baits and gels and in ant bait stations.

Fipronil is also used in veterinary chemical products as a spray-on or concentrated spot-on formulation to control fleas and ticks on cats and dogs. The veterinary chemical use of fipronil has been registered since 1995. Details of all active approvals and product registrations current at the commencement of the review are provided in Appendix 1.

2.2 Current use patterns

Veterinary chemical products containing fipronil are marketed for use on cats and dogs as ready-to-use spray or concentrated spot-on formulations. The products may be applied monthly for flea control or every two weeks for tick control. Two products also include the active (S)-methoprene and are recommended for the control of fleas and biting lice as well as the treatment and control of allergy dermatitis.

In agriculture, products containing fipronil are widely used as an insecticidal seed dressing in rice, canola, sorghum and cotton, as ultra low volume (ULV) sprays to control locusts in pasture and sorghum and as sprays to control a wide range of insect pests in bananas, brassica, cotton, potatoes, sugarcane and in mushroom production where it is applied to the peat moss. A granular formulation is registered for use in recreational, domestic and commercial turf. Fipronil is also included in a number of household products and commercial building treatments such as cockroach baits and gels and in ant bait stations.

3. REASONS FOR THE RECONSIDERATION OF APPROVALS AND REGISTRATIONS RELATING TO FIPRONIL

The decision to review and reconsider the active fipronil and products containing fipronil and their labels stems from concerns over human health and animal safety.

The APVMA has received a number of adverse experience reports involving products containing fipronil. Reports include 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.

In view of these reports the APVMA will consider whether fipronil and products containing fipronil in the context of both agricultural and veterinary uses:

- may be an undue hazard to the safety of people exposed to it during their handling;
- may have an effect that is harmful to human beings;
- may have an unintended effect that is harmful to animals; and whether
- product labels contain adequate instructions with regard to the safe handling of the product or other warning and precautionary instructions.

Further details in relation to these concerns are provided in this document.

4. SCOPE OF THE REVIEW

The APVMA will review the following matters relevant to active constituent approvals, product registrations and label approvals for fipronil:

- toxicity of fipronil primarily in relation to dermal irritation and the induction of skin sensitisation;
- 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; risk to workers on re-entry to treated areas or humans handling animals after they have been treated;
- animal safety;
- adequacy of label instructions including suitability of personal protective equipment, specified re-entry intervals and other warnings or precautionary instructions.

Registrants and approval holders will be required to undertake certain actions aimed at securing relevant data that might address these matters. However, the public is invited to make submission to the review regarding any of the matters raised in this scope document (see Section 10).

5. SUSPECTED ADVERSE EXPERIENCE REPORTS

The AVPMA's Adverse Experience Reporting Program (AERP) has recorded adverse experience reports for products containing fipronil, primarily in veterinary chemical products. Note that the AVPMA does not have a formal adverse experience reporting program for agricultural products at this time.

Continuing receipt of such reports at a steady rate, particularly over the past three years has raised concerns about the safety of fipronil. When compared to the number of doses sold the incidence of adverse experience reports for products containing fipronil are relatively low (<0.01%). However, these reports have raised concerns in relation to target/non-target animal safety. In addition, some of the reports involve suspected adverse reactions in humans.

The first reports of adverse effects in humans were received in 1996 for the veterinary spray formulation and involved reactions in humans who had applied the spray to pets. Since then, 53 reports of suspected adverse effects in humans involving both the spray and the concentrated spot-on formulation have been received (Table 1). Of these reports 43 have been considered by the APVMA as possibly or probably linked to product use. The link to product use is considered to be "unlikely or unknown" for the remaining ten reports (Table 2).

Skin reactions are the predominant adverse experience reported for pet owners. Some reactions did not occur during the application of the products but after skin contact with the treated cat fur or dog hair.

One adverse experience report was received in 1999 for an agricultural product from an aerial applicators' association.

Reports of adverse effects in animals were first received in 1997 and have been recorded in every reporting period since then (Table 1). Of the 120 animal reports to date 80 have been classified by the APVMA as possibly or probably linked to product use on cats and dogs. A further 27 reports have been linked to off-label product use in rabbits (Table 2).

Clinical signs reported in animals include skin reactions and neurological signs followed in some cases by death. In Australia there have been 56 suspect 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, 9 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 2 cases neurological excitation without death was reported. In the remaining cases a range of adverse effects including skin reactions have been reported.

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

Table 1: Reports of suspected adverse experience reports following use of veterinary spray and veterinary spot-on formulations (1996-to date).

	Reports Received by the APVMA																
	1996		1997		1998		1999		2000		2001		2002		2003		Total
	spot	spray	spot	spray	spot	spray	spot	spray	spot	spray	spot	spray	spot	spray	spot	spray	
Human	0	2	2	1	5	0	13	0	5	2	6	1	16	0	0	0	53
Canine	0	0	11	3	27	6	3	1	5	1	4	1	1	2	0	1	66
Feline	0	0	4	1	9	1	0	0	4	0	5	0	2	0	1	0	27
Rabbit	0	0	0	0	7	3	2	3	1	1	3	1	6	0	0	0	27
Total	0	2	17	5	48	10	18	4	15	4	18	3	25	2	1	1	173

Table 2: Classification of adverse experience reports for veterinary spray and veterinary spot-on formulations.

	Adverse experience reporting classification				Total
	Probable	Possible	Unlikely	Unknown	
Human	12	31	6	4	53
Canine	15	41	8	2	66
Feline	8	16	3	0	27
Rabbit	27	0	0	0	27
Total	62	88	17	6	173

More information regarding the AERP for Veterinary Chemical Products and specific details on the adverse experience reports pertaining to fipronil can be obtained from the APVMA web page www.apvma.gov.au/qa/aerp.shtml

6. TOXICOLOGICAL ISSUES

Fipronil is a member of a relatively new class of pesticide known as phenylpyrazoles. Fipronil disrupts normal nerve function by blocking gamma-aminobutyric acid (GABA)-gated chloride channels of neurons in the central nervous system. The GABA-receptor system is responsible for inhibition of normal neural activity (as it prevents excessive stimulation of the nerves). When the system's regular functions are blocked by fipronil, the result is neural excitation and death. Although fipronil is selectively toxic to insects, some of the toxicity of fipronil observed in mammals also appears to involve interference with the normal functioning of neuro-receptors. A toxicological assessment of fipronil and products containing fipronil conducted by the Therapeutic Goods Administration in 1996 found that fipronil has moderate acute toxicity and did not irritate the skin or eyes of rabbits or cause skin sensitization in guinea pigs. Two products containing fipronil were found to have caused slight skin irritation in rabbits, weak skin sensitization in guinea pigs and slight to moderate eye irritation in rabbits (Public Release Summary of the evaluation of fipronil in the products Regent 200SC Insecticide and Presto Mushroom Insecticide, APVMA 1995).

The predominant adverse effects experienced by the pet owner may involve an immune-mediated response. This response is not reported to occur during the application of the products but following skin contact with the treated cat fur or dog hair. Products containing fipronil have also been associated with a number of animal deaths. Neurological signs preceded these deaths. Such cases often involved infestation with paralysis ticks.

The toxicology of fipronil was reviewed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1997 with additional information published in 2000.

7. OCCUPATIONAL HEALTH AND SAFETY ISSUES

The existing toxicological database does not predict an immune-mediated reaction in humans or the incidences of dermal reactions in animals. Both these parameters are relevant to worker exposure and additional toxicological information may have an impact on previous recommendations for products containing fipronil. Given the identified concerns related to the risk of sensitisation and human/worker safety aspects the occupational health and safety risk assessment will review the adequacy and suitability of the existing label instructions, particularly those related to Personal Protection Equipment (PPE), the specified re-entry intervals and the need for re-handling statements.

8. ANIMAL SAFETY ISSUES

Adverse experiences involving veterinary chemical products containing fipronil have been reported regularly since the products were first registered. Patterns that appear to have emerged involve the development of certain clinical signs including skin reactions, neurological signs, lethargy, anorexia and in some cases death. In Australia there have been 56 suspect 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, 9 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 2 cases neurological excitation without death has been reported. In the remaining cases a range of adverse effects including skin reactions have been reported.

The safety assessment will review the adverse animal experience reports in light of existing and new animal safety studies (margin of safety studies, tissue irritation studies as well as adverse experience records during clinical trials plus reports of experiences in use). The assessment will determine the adequacy of label instructions specifically in regard to warning or precautionary instructions.

9. INTERNATIONAL REGULATORY STATUS OF FIPRONIL

Products containing fipronil for use in agriculture or on animals are registered world-wide. In the United States, the Department of Pesticide Regulation (California 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.

10. SUBMISSIONS FROM THE PUBLIC INVITED

The formal review will now commence and will deal with the aspects outlined in this scope document.

Interested parties are invited to provide data or information addressing the matters outlined in Section 3 of this scope document. These must reach the APVMA no later than **31 January 2004**. Submissions can be sent electronically by email to chemrev@apvma.gov.au or by mail to:

Manager, Veterinary Medicines Review
Australian Pesticides & Veterinary Medicines Authority
P.O. Box E240
KINGSTON ACT 2604
Telephone: (02) 6272 3213

11. DATA ASSESSMENT AND POSSIBLE OUTCOMES

The technical assessment of data submitted for the review of fipronil will be conducted by the Therapeutic Goods Administration (TGA), the National Occupational Health and Safety Commission (NOHSC) and an external expert who will advise on animal safety issues.

Depending on the findings of the technical assessment a review can result in one of three broad outcomes.

- The APVMA is satisfied that active constituents and products containing fipronil continue to meet the conditions to which registration or approval are currently subject and confirms the registration and approvals; or

- The APVMA is 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 or approval will be complied with, and varies the conditions of approval or registration; or
- The APVMA is not satisfied that the conditions continue to be met and suspends or cancels the registration or approvals.

The data might lead agencies that provide expert advice to the APVMA to consider setting appropriate public health standards, which in this case might involve:

- the Office of Chemical Safety revising the Acceptable Daily Intake (ADI)
- the National Drugs and Poisons Scheduling Committee revising the existing poisons schedule
- the Office of Chemical Safety revising the acute reference dose

The APVMA will have regard to the appropriate public health standards in its reconsideration of approvals and registrations.

12. CONSULTATION THROUGHOUT THE REVIEW PROCESS

From initiation of the review through to the implementation of the review outcomes, the APVMA will consult with relevant stakeholders and interested parties. Prior to finalisation of any review outcomes comments from key stakeholders and the public will be sought.

The draft of the review summary along with proposed outcomes will be made available to stakeholders and the public through the APVMA website or via direct communication. A period will be given for these groups to comment on the draft report.

Table 3: Active constituent approvals for fipronil

Approval number	Name	Approval holder
46789	Fipronil	Bayer Cropscience Pty Ltd
49120	Fipronil manufacturing concentrate	Bayer Cropscience Pty Ltd
51985	Fipronil	Bayer Cropscience Pty Ltd
52547	Fipronil manufacturing concentrate	Bayer Cropscience Pty Ltd

Table 4: Registered veterinary products containing fipronil

Product number	Product name	Registrant
46828	Frontline Spray	Merial Australia Pty Ltd
48523	Frontline Top Spot Cat	Merial Australia Pty Ltd
48606	Frontline Top Spot Small Dog	Merial Australia Pty Ltd
49825	Frontline Top Spot Medium Dog	Merial Australia Pty Ltd
49826	Frontline Top Spot Large Dog	Merial Australia Pty Ltd
51304	Startgard For Puppies	Merial Australia Pty Ltd
51530	Startgard For Kittens	Merial Australia Pty Ltd
52043	Frontline Top Spot Extra Large Dog	Merial Australia Pty Ltd
52327	Frontline Top Spot For Dogs	Merial Australia Pty Ltd
54523	Frontline Plus (Fipronil Plus (S)-Methoprene) For Dogs	Merial Australia Pty Ltd
54524	Frontline Plus (Fipronil Plus (S)-Methoprene) For Cats	Merial Australia Pty Ltd
56123	Startgard Plus for Puppies	Merial Australia Pty Ltd
56124	Startgard Plus for Kittens	Merial Australia Pty Ltd

Table 5: Registered agricultural products containing fipronil

Product number	Product name	Registrant
46793	Regent 200SC Insecticide	BASF Australia Ltd
47407	Regent 800WG Insecticide	BASF Australia Ltd
48921	Chipco Choice Insecticide	BASF Australia Ltd
49434	Cosmos Insecticidal Seed Treatment	BASF Australia Ltd
49646	Goliath Cockroach Bait	BASF Australia Ltd
49647	Goliath Cockroach Gel	BASF Australia Ltd
50285	Adonis 8.5ul Insecticide	BASF Australia Ltd
51371	Semevin Super Seed Dressing Insecticide	BASF Australia Ltd
51720	Combat Ant-Rid Relief From Tough Ant Problems 4 Ant Baits	Clorox Australia Pty Ltd
53156	Adonis 3ul 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
54624	Termidor Residual Termiticide	BASF Australia Ltd
55553	Maxforce Gold Gel Insecticide	Bayer Cropsciences Pty Ltd
57764	Impede Insecticide	BASF Australia Ltd