briefing paper

Pesticide Action Network UK

Health and environmental effects of fipronil

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Fipronil is an insecticide discovered and developed by Rhône-Poulenc between 1985-87 and placed on the market in 1993. Although effective against a variety of pests, there are concerns about its environmental and human health effects. Actively marketed in many industrialised and developing countries, its worldwide use is increasing.

Introduction

Fipronil is a commercial insecticide discovered and developed by Rhône-Poulenc between 1985-87 and placed on the market in 1993. It is a member of a relatively new, relatively small class of pesticides, the phenyl pyrazoles, which are principally chemicals with a herbicidal effect (Rhône-Poulenc, 1995). Fipronil, however, acts as an insecticide with contact and stomach action. It is highly effective against a variety of insect pests, but there have been concerns voiced about its environmental and human health effects. Its use worldwide is increasing and it is being actively marketed throughout a wide range of industrialised and developing countries (Anon, 2000a; 2000b; 2000c; 2000d; 2000e).

Fipronil is available in a range of formulations including water dispersible granules (WG), micro granules (GR), flowable solid (FS), soluble concentrate (SC) and Ultra Low Volume (ULV). It is sold commercially under various trade names including 'Icon' 'Regent', 'Ascend', 'Termidor' 'Goliath', 'Chipco', 'Chipco Choice' and 'Adonis' (Rhône-Poulenc, 1996; Aventis 2000a). It is also sold as a veterinary product for tick, mite and flea control on pets and domestic stock under the trade names 'Frontline' and 'Top spot' (Rhône-Poulenc, 1996).

Fipronil was the "flagship" insecticide for the company Rhône-Poulenc until the fusion of Rhône-Poulenc and AgrEvo (Hoechst) to form Aventis in the year 2000. Turnover from sales of fipronil was Fr700 M in 1996 (Anon, 1997a). Sales of fipronil-based crop protection and animal health products were estimated at over Fr1400 M in 1997 expected to rise to Fr3000 M by the turn of the century (Anon, 1997b). In 2000 it was reported that the strategic agrochemicals posted strong growth during 1999, with sales of Regent® (a fipronil-based insecticide) increasing by 38% to 168 million euros (Aventis, 2000b; Anon, 2000a).

What is fipronil?

Fipronil is a broad spectrum, low rate insecticide. The technical grade material is a white powder with a mouldy odour (USEPA, 1996) and a molecular mass of 437 (ACP, 1999). It is sparingly soluble in water (ACP, 1999); stable at normal temperatures for one year but not stable in the presence of metal ions. It is degraded by sunlight to produce a variety of metabolites, one of which (fipronil-desulfinyl (MB 46513)) is extremely stable and is more toxic than the parent compound (USEPA, 1998a).

Production

In 1997, production was around 480 tonnes per annum, expected to rise to 800 tonnes by the end of the century (Anon, 1997b).

Manufacture and transport

Production takes place at the Rhône-Poulenc Biochimie plant at Saint-Aubin-Lès-Elbeuf, France. The 3,500 m^2 plant consists of 2 buildings, nine reactors, 2 filters and 2 dryers (Anon, 1997b).

The Joint Venture project between Aventis CropScience and HangZhou General Pesticide Plant for the production of the Aventis CropScience fipronil insecticide has cleared the last stage in the Chinese approval process. The entire project represents a total investment of 50 million Euros. The new company will ensure the synthesis, formulation and distribution for the new insecticide Regent® on the Chinese market, as well as for some other Aventis CropScience products (Aventis, 2000c).

Aventis's production in Brazil is to be centred at the ex- Rhône-Poulenc site in Portão. In Columbia, production has transferred to Carthagena and to Rhône-Poulenc's old site at Apodaca. Aventis's leading products in Latin America include fipronil (Anon, 2000f).

Occupational exposure during manufacture, formulation and disposal

Few issues under this heading will be unique to fipronil, apart from actual data on occupational

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Fipronil ... is a potent disrupter of the insect central nervous system via interference with ... the passage of chloride ions through the gamma-aminobutyric acid (GABA) regulated chloride channel.

exposure. Guidelines for the safe formulation and packing of pesticides and on safe warehousing are available and should be adhered to strictly by the companies responsible (GIFAP, 1982; 1988; 1993).

Five teams of seven multi-skilled staff operate the production plant at St.-Aubin-Lès-Elbeuf, 24 h/day. 30% of the $84 million total cost of construction of the production complex was spent on safety measures (e.g. automated packaging) to avoid staff coming into contact with the active ingredient (Anon, 1997b).

Formulation of the fipronil based products Goliath and Termidor takes place at the plant at Bangpoo near Bangkok, Thailand, which is soon to be upgraded with a prospective staff of 105 people (Anon, 2000b). Formulation also takes place at the plant in L'Aquila, Italy, with a workforce of about 300. Leading products in Italy include Regent (Anon, 2000f).

No information on exposure of workers or others to fipronil during manufacture or product formulation was provided for registration of fipronil-based products as a public hygiene insecticide in the UK (ACP, 1999). No information on occupational exposure provided by the company has been found throughout the search for literature on fipronil.

Mode of action

Fipronil is an extremely active molecule and is a potent disrupter of the insect central nervous system via interference with the passage of chloride ions through the gamma-aminobutyric acid (GABA) regulated chloride channel (Rhône-Poulenc, 1996). This results in uncontrolled central nervous system activity and subsequent death of the insect (FAO, 1998). Despite the fact that the GABA channel is important in nerve transmission in both vertebrate and invertebrate animals (Grant *et al*., 1990), and that fipronil does bind to the GABA receptor in vertebrates, the binding is "less tight" which offers a degree of selectivity (Rhône-Poulenc, 1995; Grant *et al*., 1998).However, some of the toxicity of fipronil observed in mammals also appears to involve interference with normal functioning of the GABA receptor (FAO, 1998).

No resistance to fipronil has so far been recorded. However ... a resistance mechanism to fipronil may already be present in German cockroach field populations.

Resistance and cross-resistance

No resistance to fipronil has so far been recorded.However, although fipronil effectively killed laboratory-reared German cockroaches when applied in nanogramme quantities, field-collected strains were significantly more tolerant of fipronil than the laboratory strains. This suggests that an insecticide resistance mechanism to fipronil may already be present in German cockroach field populations. Furthermore, it was determined that German cockroaches metabolically activate (make more toxic) fipronil in their bodies (Valles *et al*., 1997).

The other groups of insecticides that have a similar mode of action are the Cyclodiene group of organochlorines - aldrin, endrin, dieldrin, etc.. These also act on the GABA reception in nerve transmission, but there are differences in the binding sites of the two classes of insecticide which suggest that cross-resistance (although not impossible) is unlikely to occur (Rhône-Poulenc, 1995). Decreased biological activity of fipronil against dieldrin resistant houseflies (LC_{50} 36 mg/l) by comparison with a dieldrin susceptible strain (LC_{50} 0.4 mg/l) has been reported by the manufacturers (Colliot *et al*., 1992) and also noted in later trials (Cole *et al*., 1993; Bloomquist *et al*., 1999). Some cross-resistance has also been recorded in the Cld-R strain of German cockroach which is 6.7-7.7-fold cross-resistant and in LPR and OCR strains of houseflies, which are 15- and 31-fold cross-resistant, respectively (Scott & Wen, 1997). Apparent cross-resistance exhibited by field populations of German cockroaches toward fipronil question its long-term utility for use against these insects (Valles *et al*., 1997), nevertheless no cross-resistance to fipronil was noted in Chlordane resistant cockroaches (Bloomquist *et al*., 1999).

Antagonism and synergism

Fipronil is 2.2-3.0 times less toxic to German cockroaches pre-treated with piperonyl butoxide or S,S,S-tributyl phosphorotrithionate (Valles *et al*., 1997). Similar antagonism with piperonyl butoxide has been recorded in some studies (Cole *et al*., 1993; Scharf & Siegfried, 1997) but not in others (Scott & Wen, 1997).

Verbutin (MB-599) shows positive synergism with fipronil (Szekely *et al*., 1996).

Usage

Crop protection accounted for about 39% of total fipronil production in 1997 (Anon, 1997b).

Between 1987 and 1996 fipronil was evaluated on more than 250 insect pests on 60 crops worldwide. It is highly effective against the cotton boll weevil (*Anthonomus grandis*) and in field trials against cotton boll weevil, fipronil also provided suppression of secondary pests *Heliothis (Helicoverpa) virescens, Spodoptera* spp. and *Alabama argillacea* (Hamon *et al*., 1996).

Fipronil is marketed for use against major lepidopteran and orthopteran pests on a wide range of field and horticultural crops and against coleoptera larvae in soils. It is also employed for flea and tick control on household pets, and for cockroach and ant control. Major agricultural uses include granular applications at 30-100 g a.i./ha on rice for the control of rice stem borers (*Chilo* spp. *Tryporyza* spp.), brown plant hopper (*Nilaparvata lugens*) and rice water weevil (*Lissorrhoptus orzyophilus*). Foliar applications at rates of 12.5-50.0 g ai/ha are used against diamondback moth (*Plutella xylostella*), Colorado potato beetle (*Leptinotarsa decemlineata*), cotton boll weevil (*Anthonomus grandis grandis*), cabbage looper (*Trichoplusia ni*), cabbageworm (*Pieris rapae*) and thrips (*Frankliniella* spp.) (Rhône-Poulenc, 1996).

Fipronil has also been used for locust control in Madagascar (World Bank, 1998; LeCoq, 2000) and Kazakhstan (AAAI, 2000), following trials in the USA (Lockwood *et al*., 1998), Brazil (LeCoq & Balança, 1998) and West Africa (Rachadi & Foucart, 1999). Field trials have also been undertaken against locusts in Australia (APLC, 1999; 2000; Hunter & Spurgin, 2000; Spurgin, 2000) and Russia (Latchininsky, 2000). The persistence of the parent compound and its metabolites has made it especially suited for locust hopper[1] control, but this factor associated with its relatively slow speed of action against adult locusts have led to recommendations against its use for locust swarm control (World Bank, 1998).

Fipronil is registered in the USA for use on field corn, on golf course and commercial turf (USEPA, 1996), on pets, and in cockroach and ant bait stations (USEPA, 1998). It has also shown promise as an ant bait toxicant in trials in Czechoslovakia (Rupes *et al*., 1999).

Fipronil is also a powerful termiticide and was shown to be effective in field trials in South Africa (PPRI, 1997), Zimbabwe (Rattan & Mukubareza, 1997), Africa (Tran Van Cahn *et al*., 1998), the USA (Henderson & Forschler, 1997) and Australia (Ahmed *et al*., 1997). It is marketed under the name "Termidor" (Anon b., 1997).

Fipronil is effective as a seed coating to control thrips (Ester *et al*., 1997). It is also permitted for use as a spray at 200 ml/ha (Regent 200SC - 200 g/l) on ornamental crops against Western Flower thrips in Australia (AFFA, 2000).

In 1994 and 1995 fipronil (Regent) was applied in small plot evaluations to determine it's effectiveness in controlling cotton flea hoppers (*P. seraltus*). In 1994 under moderate insect pressure, Regent at 0.038 and 0.05 lb a.i./acre performed as well as the commercial curacron (profenofos) standard. There was no apparent rate response. In 1995 under lighter insect pressure, Regent at 0.05 lb a.i./acre reduced the number of nymphs over both the untreated and the Orthene (acephate) standard. The Regent treatments showed a rate response over the entire trial with the 0.05 lb a.i./acre rate outperforming the 0.038 lb a.i./acre rate (Holmes & Hopkins, 1997).

Fipronil is identified as a promising new candidate in the control of the sugarcane froghopper, as part of an IPM program involving aerial applications of insecticide and fungal spores of *Metarhizium anisopliae* (des Vignes, 1997). However, this result conflicts with the findings of Moino & Alves (1998) who found fipronil to be toxic to this fungus (see **IPM compatability**).

Table 1. Biological activity of fipronil and cypermethrin against a variety of insects[2] measured by LC_{50}[or '*' LC_{90}] in mg/l (Colliot *et al*., 1992)

Species [and stadium at initiation of test]	**Fipronil**	**Cypermethrin**
Aphis gossypii [MP]	1.2	0.1
Niliparvata lugens [L]*	0.2	0.5
Nephotettix cincticeps [L]*	5.0	5.0
Spodoptera eridania [L2]	4.0	2.0
Spodoptera frugiperda [L2]	3.6	1.6
Plutella xylostella [L2]*	0.3	0.4
Heliothus[3] *virescens* [L2]	4.3	30
Heliothus[3] *armigera* [L2]*	10.0	0.4
Helicoverpa zea [L2]	1.8	1.4
Leptinotarsa decemlineata [L]	0.03	0.23
Musca domestica [A]	0.39	5.0
Diabrotica virgifera [E]	0.03	-

Key: MP = mixed population (adults + nymphs); L = larva/nymph (mixed instars); L2 = 2nd instar larva; A = adult; E = egg.

In 1999, 400 000 hectares were treated with Regent. It became the leading imported product in the area of rice insecticides, the second biggest crop protection market after cotton in China (Aventis, 2000c).

Fipronil has also shown promise in mosquito control trials in the laboratory (Ali *et al*., 1999).

Fipronil was effective in curing a budgerigar of lice (Beck, 1999).

Fipronil is also used to control fleas, lice, ticks and mites on domestic animals (Chadwick, 1997; Jacklin, 1997; Araujo *et al*., 1998; Cutler, 1998; Nuttall *et al*., 1998; Bordeau, 1998; Hermann *et al*., 1998; Beck, 1999b; Davey *et al*., 1999; Hugnet *et al*., 1999), following trials on a good many pets and stock animals (Postal *et al*., 1995; Atwell, Postal *et al*., 1996; Atwell, Sillar *et al*., 1996; Cooper & Penaliggon, 1996; Cochet *et al*., 1997; Harvey *et al*., 1997; Song, 1997; Penaliggon, 1997; Hutchinson *et al*., 1998). Fipronil does not prevent fleas from feeding on pets, before being killed by the insecticide (Franc & Cadiergues, 1998). When topically applied, it was found to be less effective against dog ticks than an amitraz-impregnated collar (Estrada-Pena & Ascher, 1999).

Biological activity

Biological activity of fipronil against corn root worm (*Diabrotica* spp.) is recorded as very high (LD_{50} = 0.33 ng/mg), but is reduced in the presence of piperonyl butoxide (Scharf & Siegfried, 1999).

Larvae of two *Heliothis*[3] species were collected from the field and assayed for susceptibility to various insecticides using a diet bioassay. Fipronil had good activity against both species. In general, the 96h activity spectrum for the compounds tested were: spinosad > Pirate R > fipronil > cypermethrin > MVP II R (Hasty *et al*., 1997).

The biological activity of fipronil to a wide variety of insects[2] is presented in Table 1.

Regulatory issues

Since 1993 Regent has been registered for use in rice in several Asian countries including Indonesia, Vietnam, the Philippines, Thailand, China, Taiwan, Malaysia, Japan, Korea and India. It is also registered and used in Europe in other crops such as maize and sunflower (Rhône-Poulenc, 1997). By the end of 1995 it was registered in an additional 9 countries in south and central America, 3 in Africa and 2 in the Caribbean for use on specific crops, plus 30 countries (including France, the UK (Bond, 1998), Australia and Brazil) for flea and tick control on pets (Rhône-Poulenc, 1996). By the end of 1997, fipronil was registered for non-agricultural use in 63 countries and for agricultural use in 51 countries (Belayneh, 1998).

By the end of 1997, fipronil was registered for non-agricultural use in 63 countries and for agricultural use in 51 countries.

Fipronil has a temporary permit for use on ornamental crops against western flower thrips in Australia until May 2000 (AFFA, 2000).

Fipronil is registered in the USA for use on maize, on golf course and commercial turf (USEPA, 1996),

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[1] Immature locusts or nymphs, which are flightless because wings have yet to be fully developed.

[2] For all these insects the technical AI was diluted in 5% acetone + 95% water and sprayed onto host plants either pre or post infested. Exceptionally, Fipronil was added to 10% sucrose and provided ad libitum to adult *Musca domestica*. Fipronil diluted in 1% acetone + 99% water was added (m/m) to soil containing both maize seeds and *D. virgifera* larvae.

[3] Now *Helicoverpa*.

> Registration of Frontline spray treatment for cats and dogs was denied in New York State ... "based on the significant exposure potential of fipronil to commercial pet groomers and the toxicological properties of fipronil".

on pets, and in cockroach and ant bait stations (USEPA, 1998). The year of initial Registration was May 1996 for Chipco Choice (USEPA, 1996).

However, registration for use on cotton in Mississippi, rangeland in Wyoming and rice in Louisiana has either been denied or withdrawn (USEPA, 2000). Registration of Frontline spray treatment for cats and dogs was denied in New York State by New York State Department of Environmental Conservation, Division of Solid and Hazardous Materials in 1996 and again in 1997 "based on the significant exposure potential of fipronil to commercial pet groomers and the toxicological properties of fipronil" (Nosenchuck, 1997).

In the UK, provisional approval for 5 years has been granted by the Advisory Committee on Pesticides (ACP) of the Pesticides Safety Directorate (PSD) for fipronil use as a public hygiene insecticide (ACP, 1999). However, only an experimental approval for use of another product containing fipronil has been granted, because of data gaps (ACP, 2000) (see below).

Application technology

Because of the wide range of available formulations, fipronil may be applied by any conventional application equipment. Examples of the range of possibilities include:

- Efficacy tests of ultra low volume (ULV) and high volume application tests of fipronil against the cotton boll weevil in Texas concluded that fipronil is highly effective in either ULV sprays at 0.043 and 0.056 g.ai/ha, or as high volume sprays in water at 0.028, 0.056 and 0.084 g.ai/ha (USEPA, 1996).
- The effectiveness of a citrus meal and fipronil bait for the control of the leaf-cutting ants *Acromyrmex octospinus* (Reich.), and *Atta cephalotes* (L) in Trinidad and Tobago showed that baits containing 2% a.i. of fipronil provided satisfactory control (White, 1998)
- The efficacy of a granular formulation of fipronil (Regent 3G), a 5% w/w suspension concentrate of fipronil (Regent 50 SC) and *B. thuringiensis* H-14 (subsp. *Israelensis*) against the dengue vector *Aedes albopictus* in discarded tyres, showed

Application rates

Table 2. Application rates for fipronil against different pest species

Application rate (g a.i./ha)	**Formulation**	**Target pest**	**Efficacy**	**Reference**
0.6-2	ULV	grasshoppers	High but slow	Balança & De Visscher, 1997a
0.6-1.25	ULV	locust	Effective	Hunter & Spurgin, 2000
1.04-1.96	ULV- barriers	locust	Effective	Rachadi & Foucart, 1999
1.25-2.5	ULV	Migratory locust	Effective	APLC, 1999; 2000
3.08	ULV- barriers	grasshoppers	Effective but slow	Latchininsky, 2000
4	ULV- barriers	locust	Effective	Latchininsky, 2000
2.15-11.8	spray	locust	v. high	Lecoq & Balança, 1998
4.2-13.4	ULV	locust	Good-excellent	Balança & De Visscher, 1997b
12.5-50	spray	Dbm, cpb, cbw		Rhone-Poulenc, 1996
20.2-42.6	spray	Cbw, tpb	Effective	Scott *et al*., 1997
25-50	spray	Cpb, dbm, cbw	Effective	Colliot *et al*., 1992
28-42.6	spray	thrips	Effective	Christian *et al*., 1997
42.6-56	spray	Lygus bugs	Effective	Shaw *et al*., 1997
50		Bph, rww	Excellent	Colliot *et al*., 1992
56	ULV	cbw	Effective	Tillman & Mulroony, 1997
56 (x 6)	ULV	cbw	Ineffective	Sparks *et al*., 1997
56	spray	cbw	Effective	Parker & Huffman, 1997.
76.2		Lygus bugs	Effective	Teague & Tugwell, 1997
25-100		cbw		Martinez-Carrillo & Pacheco-Covarrubias, 1997
30-100	granules	rsb, bph, rww		Rhone-Poulenc, 1996
120		Crw, wireworm	Effective	Colliot *et al*., 1992
100-200		Crw, wireworm	Good	Colliot & Morgan, 1993
200 g/l (0.2 l/ha)	spray	wft		AFFA, 2000
50 g/unit seed	Seed coat	thrips	Good	Ester *et al*., 1997
	drench	termites	Good	Rattan & Mukumbareza, 1997
0.1-10 ppm	bait	termites	Effective	Henderson & Forschler, 1997
5-200 ppm	Timber treatment	termites	Good-excellent	Ahmed *et al*., 1997
25.5-51	15mg/mg bait	ants	Effective	Collins & Callcott, 1998

Rsb = rice stem borer; Bph = Brown plant hopper (*Niloparvata lugens*); Tpb =tarnished plant bug (*Lygus lineolaris*); Rww = rice water weevil (*Lissorhoptrus oryzophilus*); Dbm = diamond back moth (*Plutella xylostella*); Cpb = Colorado potato beetle (*Leptinotarsa decemlineata*); Cbw = cotton boll weevil (*Anthonomus grandis*); Crw = corn root worm (*Diabrotica* spp.); Wft = western flower thrips that fipronil granules was the most effective larvicide having a residual activity of up to two weeks with >80% activity (Sulaiman *et al*., 1997).

Fipronil degrades slightly when exposed to direct sunlight. It is stable at normal room temperatures for one year in the absence of metallic ions.

Efforts to identify pesticides that were more appropriate for use with aerial electrostatic systems revealed that fipronil was favourable for taking on a high charge to mass ratio in electrostatic systems. Aerial applications of label rates of Regent 2.5 EC insecticide were made on a sixteen-acre cotton field located in Burleson County, Texas. Electrostatic applications of fipronil gave significantly higher weevil mortalities than the ULV malathion treatment on day-3 after spraying. Spray deposits were higher for the electrostatic applications of fipronil than with ULV malathion. Fipronil in 12 oz oil/acre had lower deposits on oil sensitive papers than ULV malathion (Kirk, undated).

Environmental fate

Fipronil degrades slightly when exposed to direct sunlight. It is stable at normal room temperatures for one year in the absence of metallic ions. After storage for one day at 100 °C, and seven days at 50 °C, decomposition was found to be less than 0.5%. Fipronil degrades to a number of metabolites, depending on the conditions, with no volatility (Belayneh, 1998).

The half life of fipronil incorporated in soil ranged from 3.0 to 7.3 months with more than 90% ... residues being found in the upper 30 cm of soil.

Under aerobic conditions, fipronil is slowly degraded through oxidation, reduction and hydrolytic pathways. The three main metabolites under aerobic conditions are RPA 200766 (amide), MB 46513 (fipronil-desulfinyl) and MB 46136 (sulfone, oxidation). Under anaerobic conditions, fipronil degrades into MB 45950 and RPA 200766. In laboratory studies, the half life ($t_{1/2}$) of fipronil in various soils maintained at 22-25 °C under aerobic conditions, was 18-308 days (Table 3) depending on soil type, pH and organic matter (OM) contents (Belayneh, 1998).

Laboratory data indicate that, below the soil surface, fipronil dissipates by binding to the soil followed by slower biotic mediated processes. On the soil surface the major degradation pathway may be slow photolysis and/or soil binding, again followed by slower biotic mediated processes.

Table 3. Fipronil degradation rates in soil

Soil type	pH	Temperature oC	OM %	Half life of fipronil (days)
Sandy loam	7.8	25	1.7	28
Sandy loam	6.4	22	0.75	117
Sandy clay loam	6.2	22	1.2	18
Sandy clay loam	6.2	22	2.2	40
Sand	6.1	25	3.3	308
Sand	6.3	22	5.7	62

Fipronil residues tend to stay in the upper 15 cm of soil and exhibit low potential to leach to groundwater. Of the major degradates identified in laboratory studies, only two (MB 46136 and RPA 200766) were found in field studies at amounts greater than the limit of detection (Belayneh, 1998; Mulrooney *et al*., 1998). The lab data were supported by terrestrial field studies which have shown that fipronil dissipates with a half-life of 1.1 to 1.5 months on bare soil and 0.4 to 0.5 months for turfed soil (Mulrooney *et al*., 1998).

In studies carried out in Europe and the USA the half life of fipronil incorporated in soil ranged from 3.0 to 7.3 months with more than 90% of the measured residues being found in the upper 30 cm of soil. A field dissipation study on established turf at two sites in the USA where fipronil was applied using a slit applicator at a rate of 56 g ai/ha gave an estimated half-life for fipronil of 0.4 to 1.5 months (Rhône-Poulenc, 1996).

A field study concluded that fipronil degrades faster under tropical conditions than temperate and that the majority of the metabolites belonged to the photodegradate desulfinyl (Belayneh, 1998).

In field studies carried out in Niger in 1995 fipronil applied as a spray to the surface of a sand/silt soil was found to have a half-life of 36 hours in the upper 10 cm soil layer. Three days after soil treatment, fipronil had been degraded by 75% with the corresponding appearance of the metabolites MB 45950, RPA 200766, MB 46513 and MB 46136 (Bobé *et al*., 1998).

Photodegradation

Soil

Fipronil degrades slowly on loamy soil when exposed to light, with a half-life of 34 days. Three major degradates have been identified, RPA 200766 (amide), MB46513 (fipronil-desulfinyl), and RPA 104615. No evidence of volatility of fipronil or its metabolites was found (USEPA, 1996; Mulrooney *et al*., 1998). Of the major degradates identified in the laboratory studies, only two, the sulfone and the amide were found at amounts greater than the limit of detection in field studies conducted under temperate climatic conditions (Belayneh, 1998).

Water

Fipronil exposed to sunlight in water has a half-life of 3.6 h (8 hours @ pH 5 and 25°C) with the major degradates being desulfinyl (MB 46513) and RPA 104615 (Belayneh, 1998). Fipronil has a half-life of 3.63 hours when exposed to a xenon light source in the laboratory. The major degradates were MB 46513 and RPA 104615 at 43% and 8% of applied radioactivity. No volatile compounds were found (USEPA, 1996).

Microbial degradation

Fipronil is slowly degraded by biotic (microbial) processes in the soil to more active and inactive by-products. Half lives for technical grade fipronil were relatively longer on bare soil than turfed soil, which suggests that microbial degradation may be responsible.

Aerobic soil metabolism.

Under aerobic conditions, soil organisms slowly break down fipronil. The half-life in sandy soil loam soil is 122-128 days, whereas in loamy sand soil was found to be 308 days (ACP, 1999). Several metabolites have been identified, including RPA 200766 and MB 46136 (sulfone) (Mulrooney *et al*., 1998) which account for 27%-38% and 14-24% of

Fipronil does not accumulate in the abiotic environment ... but metabolic studies showed ... a potential for bioaccumulation of the photodegradate MB 46513 in fatty tissues.

total applied radioactivity, respectively (USEPA, 1996).

Anaerobic aquatic metabolism.

Fipronil degrades slowly in water and sediment under anaerobic conditions. The half-life is 116 (HPLC data) - 130 (TLC data) days, although an average figure of 123 days is acceptable. Half life values determined by HPLC were considered more accurate due to the close proximity of the bands (ACP, 1999).Two major metabolites were found, MB 45950 and RPA 200766, at maximum concentrations of about 47% and 18% of applied radioactivity, respectively. MB 45950 was found in the soil extracts and RPA 200766 was found in both soil and water (USEPA, 1996).

Hydrolysis

Fipronil is stable to hydrolysis in mildly acidic water, (pH 5-6) to neutral (pH 7) water in the dark. The results of studies conducted to determine its rate of degradation showed that in aqueous solution, in the absence of light, at an ambient temp of 22 °C, 80% of the pesticide remained unchanged after 100 days. However, under alkaline conditions, fipronil degraded faster at the rate of degradation increased with an increase in pH. At pH 9, fipronil degrades with a half-life of 28 days with the major degradation product being an amide (RPA 200766, the least toxic of fipronil's metabolites) (USEPA, 1996).

The abiotic degradation of fipronil was studied in aqueous solution and on the surface of two soils from Niger and one Mediterranean soil. The rate of hydrolysis of fipronil in solution was measured at different values of pH and temperature (Table 4) (Bobé *et al*., 1997).

Fipronil degrades slowly in water and sediment under anerobic conditions with a half life of 116-130 days. Two major metabolites result from this process, MB 45950 (sulfide), found only in soil extracts and RPA 200766, present in both soil and water (Mulrooney *et al*., 1998).

Table 4. Fipronil degradation rates by hydrolysis

pH	half life (h)
7.0 - 5.5	stable
9.0	770
10.0	114
11.0	11
12.0	2.4

Fipronil residues ... exhibit low potential to leach to groundwater.

The environmental fate of fipronil was evaluated under California growing conditions to determine suitability for use. Field persistence is low-moderate in water and soil ($t_{1/2}$: 10-130 h water, 45-530 h soil) with desulfinyl product formed primarily in water and sulfide in soil. Laboratory studies show direct and indirect photolysis, volatilization, and hydrolysis as contributors to fipronil field dissipation. Formation of desulfinyl product from direct photolysis is of particular importance due to concerns of environmental persistence (Hainzl & Casida, 1996). Laboratory studies show susceptibility of fipronil-desulfinyl to direct and indirect photolysis, supporting the observed dissipation in rice field water. Overall, fipronil appears suitable for commercial application in flooded rice (Ngim & Crosby, undated).

Persistence in soil and water

The terrestrial field dissipation study showed that fipronil dissipates with a half-life of 1.1 to 1.5 months for bare soil and 0.4 to 0.5 months for turfed soil. Fipronil residues tend to stay in the upper 6 inches of soil, and thus exhibit low potential to leach to groundwater. Of the major degradates identified in lab studies, only two (MB 46136 and RPA 200766) were found in field studies at amounts greater than the limit of detection (USEPA, 1996).

Mobility in Soil

Leaching/adsorption/desorption.

Studies on leaching and adsorption/ desorption of fipronil showed that the technical grade fipronil and its metabolites have low mobility in the soil. Due to their high affinity to soil particles, most of the residues are contained in the top 10-12 cm of soil and leaching to ground water is practically non-existent. Studies on persistence and degradation of fipronil on vegetation and in the soil showed similar results (USEPA,1996) Other studies undertaken in aged soil showed that the majority of residual radioactivity was found in the top 6-8 cm layer, except for sandy loam, where it was located in the top 14 cm of the soil. (ACP, 1999). Studies in USA, Italy, France and Spain in a variety of soils gave a range of half-life varying from 0.4-7.3 months with movements of 0.15-0.3m (Norris *et al*., undated).

Bioaccumulation

Fipronil does not accumulate in the abiotic environment. However, it should be noted that given the relatively longer persistence of some metabolites, such as the desulfinyl, some level of accumulation is likely to occur if repeated applications were to be carried out in the same sites every year (Belayneh, 1998).

Metabolic studies showed that there was a potential for bioaccumulation of the photodegradate MB 46513 in fatty tissues (USEPA, 1998).

In rats, fipronil is rapidly metabolised and the residues widely distributed in the tissues, particularly fat and fatty tissues, where they remain in significant amounts one week after oral administration (see **Non-target impacts on wildlife: Mammals** below). Residue levels were greater with repeated low doses or a single high dose than with a single low dose. The long half-life (150-245 h in some cases) of fipronil in blood may reflect slow release of residues from fat and might suggest potential bioaccumulation of metabolic products of fipronil (FAO, 1998).

Fipronil appears to bioaccumulate in fish when exposed to treated water at a concentration of about 900 nanogrammes for 35 days. The data indicate that the residues are almost completely

> Fipronil appears to bioaccumulate in fish ... exposed to treated water at a concentration of about 900 nanogrammes for 35 days.

eliminated after 14 days depuration. Bioconcentration factors[4] were 321, 164, and 575 for whole fish, edible tissue and non-edible tissue, respectively (USEPA, 1996). Other studies also indicate some bioaccumulation of fipronil by fish exposed constantly over a 35 day period, with highest levels of accumulation in non-edible tissue. Elimination of residues from edible and non-edible portions of the fish was rapid following depuration (ACP, 1999).

Residues in food

Numerous studies have been conducted to determine residue levels of fipronil on a number of crops including vegetables, field fibre and fruit crops. The results indicated than residue levels in food crops are generally very low, often below acceptable limits (Belayneh, 1998).

Fipronil's half-life on treated surfaces has been determined at 3-7 months depending on the substrate and the habitat where it is applied. Maximum Residue Levels (MRLs) have been established for some food and fibre crops in a number of countries including Brazil and France. In Brazil, the MRL for sugarcane, cotton and rice is 0.01mg/kg and for potatoes the MRL is 0.05 mg/kg. In France, the MRL for maize, sunflower sugar beet, banana and cereal grains is 0.01 mg/kg. In the US, MRL for corn and rice are 0.2 mg/kg and 0.1 mg/kg respectively. In Japan MRL for rice is 0.01 mg/kg (Belayneh, 1998).

Fipronil residues are found on treated vegetation for longer than three weeks after the pesticide is applied at the recommended dosages. In some instances, effects of fipronil residues persist longer on treated surfaces, especially in areas with high organic matter, often manifested through a prolonged absence of soil organisms in treated areas. The presence of fipronil residues on vegetation for a prolonged period provides protection against attack from pests, including locusts and grasshoppers, however, residues on treated vegetation, including crops may affect susceptible non-targets, including beneficial organisms and humans via contact action. This may also happen from consumption of treated produce in the case of humans. Although this seems unlikely to occur as a result of the low dose rate at which the pesticide is applied, it is worth examining it in the light of the proposed ADI. It is indicated that data on residue of fipronil on sorghum treated immediately prior to harvest at 4 g a.i./ha showed that the residue levels would be approximately 0.035 mg/kg in grain and 0.0035 mg/kg in forage 7 days post treatment. Theoretical intake of residues from eating treated maize, rice, and meat and milk obtained from animals exposed to fipronil in Madagascar showed that the intake is below the ADI (Belayneh, 1998).

> 30 MRLs have been set by the USEPA for fipronil ... the highest tolerance ... is for whole milk (1.50 ppm), and the lowest for hog meat (0.01 ppm).

The USA Environmental Protection Agency (EPA) have established tolerances (maximum residue levels, MRLs) for pesticide residues on food which are published in a Federal document called the Code of Federal Regulations (CFR). Tolerances are generally set at the parts per million (ppm) level. Thirty such MRLs have been set by the EPA for fipronil, on a range of animal and crop products, the highest tolerance of which is for whole milk (1.50 ppm), and the lowest for hog meat (0.01 ppm). See Table 5 below.

Residues in drinking water

Laboratory studies were conducted to evaluate degradation of fipronil in aquatic environments under aerobic and anaerobic conditions. The results showed that fipronil residues rapidly moved from the water to the sediment with over 95% of the residues being found in or on the sediments within one week of application. Such movements were somewhat slower in the anaerobic aquatic system. Under aerobic conditions, the half life for fipronil was 15 days and under anaerobic conditions fipronil degrades slowly with a half life of 116-130 days resulting in two major metabolites, MB 45950 (reduction, in soil) and RPA 200766 (hydrolysis, in soil and water). This, could therefore be of significance in rice fields which are maintained waterlogged, and thus anaerobic, for much of the season (Bobé *et al*., 1997)

Table 5. Maximum residue levels for fipronil on foodstuffs (USEPA, 1997)

Crop	**MRL (ppm)**
Corn, Grain	0.02
Corn, field, fodder	0.30
Corn, field, forage	0.15
Eggs	0.03
Cattle, fat (Pre-S Min 5 days	0.40
Goats, fat of meat	0.40
Horses, fat	0.40
Sheep, fat	0.40
Hogs, fat of meat	0.04
Hogs, liver	0.02
Hogs, meat	0.01
Hogs, MBYP (Exc. Liver)	0.01
Cattle, liver (Pre-S min 14 days	0.10
Goats, liver	0.10
Horses, liver	0.10
Sheep, liver	0.10
Milk, fat (= N in whole milk)	1.50
Cattle, MBYP (Exc. Liver)	0.04
Goats, MBYP (Exc. Liver)	0.04
Horses, MBYP (Exc. Liver)	0.04
Sheep, MBYP (Exc. Liver)	0.04
Cattle, meat (Fat basis)	0.04
Goats, meat	0.04
Horses, meat (Pre-S)	0.04
Sheep, meat (Pre-S)	0.04
Poultry, fat of meat	0.05
Poultry, meat (Pre-S)	0.02
Poultry, MBYP (Inc. turkeys)	0.02
Rice, grain (Pre and Post-H)	0.04
Rice, straw	0.10

The potential for ground water contamination is considered low (USEPA, 1996).

Residues in the environment

Following monitoring of the aerial application of 'Adonis' (Fipronil 7.5 g/litre ULV at the scheduled rate of 10 litres per kilometre from four Micronair AU5000 rotary atomisers flown for barriers 200 metres wide, giving a nominal active ingredient application rate within the barriers of 3.75 g ai./ha) for the control of locusts in Madagascar, it was found that one hour after spraying, deposits of

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[4] The factor by which levels are concentrated by comparison with the concentration in water. There are problems in interpreting what these factors actually mean in different species under different conditions (see Moriarty, 1983. Ecotoxicology. The study of pollutants in ecosystems. Academic Press, London. 289 pp.)

fipronil on recumbent soil vegetation ranged from zero to 0.38 ppm. After 24 hours the residue levels had fallen to 0.12 - 0.15 ppm (King & Aigreau, 1999).

Table 5. Fipronil and metabolite residues (mg a.i./kg) on millet leaves over time, after treatment (Gadji *et al*., 1997)

Plot	product	Hours after treatment				
		1	24	72	168	336
1	Fipronil	3.70	1.52	1.66	0.11	0.10
	MB46136	0.06	0.23	0.06	0.14	0.40
	MB46513	0.02	0.03	0.08	0.09	1.03
	rainfall (mm)	0	10.4	23.6	50.1	51.1
2	Fipronil	0.95	0.54	0.07	0.04	<0.01
	MB46136	0.02	0.08	0.05	0.09	0.03
	MB46513	0.06	0.06	0.06	0.07	0.07
	rainfall (mm)	0	13.2	39.7	39.7	39.7
3	Fipronil	0.07	0.33	0.13	0.05	<0.01
	MB46136	0.11	0.07	0.11	0.12	0.11
	MB46513	0.08	0.06	0.04	0.06	0.08
	rainfall (mm)	0	0	1	1	12.1
4	Fipronil	1.14	1.51	0.31	0.65	<0.01
	MB46136	0.04	0.90	0.17	0.12	0.07
	MB46513	0.04	0.04	0.07	0.08	0.08
	rainfall (mm)	0	0	1	1	12.

Table 6. Fipronil and metabolite residues (mg a.i./kg) on grass over time, after treatment (Gadji *et al*., 1997)

Plot	product	Hours after treatment						
		1	24	72	168	336	504	672
C1	Fipronil	2.67	0.81	0.52	0.24	0.43	0.38	0.39
	MB46136	<0.02	<0.02	0.22	0.20	0.10	0.38	0.39
	MB46513	<0.02	<0.02	0.04	0.22	0.09	0.36	0.46
	rainfall (mm)	0	0	0	0	0	5	10
B3	Fipronil	2.79	1.00	0.49	0.53	0.22	0.28	0.15
	MB46136	0.18	0.27	0.31	0.38	0.24	0.25	0.13
	MB46513	0.23	1.10	0.04	0.47	0.05	0.78	0.08
	rainfall (mm)	0	0	0	0	0	5	10

Table 7. Fipronil and metabolite residues (mg a.i./kg) on dry leaves over time, after treatment (Gadji *et al*., 1997)

Plot	product	Hours after treatment						
		1	24	72	168	336	504	672
C1	Fipronil	0.23	0.13	0.10	0.14	0.29	0.12	<0.01
	MB46136	0.03	0.42	0.05	0.05	0.11	0.04	<0.02
	MB46513	<0.02	<0.02	<0.02	0.02	0.03	0.02	<0.02
	rainfall (mm)	0	0	0	0	0	5	10
B3	Fipronil	0.50	0.15	0.05	0.04	0.02	0.01	0.01
	MB46136	0.17	0.09	0.03	0.02	0.03	0.03	<0.02
	MB46513	0.04	0.03	0.05	0.02	<0.02	<0.02	<0.02
	rainfall (mm)	0	0	0	0	0	5	10

Table 8. Fipronil and metabolite residues (mg a.i./kg) in soil over time, after treatment (Gadji *et al*., 1997)

Plot	product	Hours after treatment						
		1	24	72	168	336	504	672
C1	Fipronil	4.7	4.1	1.9	0.3	0.5	<0.3	<0.3
	MB46136	1.5	1.1	1.3	0.6	1.4	1.1	2.1
	MB46513	<0.4	0.5	<0.4	<0.4	<0.4	<0.4	<0.4
	rainfall (mm)	0	0	0	0	0	5	10

The Locustox project recorded residues of fipronil between 1.6 and 4.1 mg a.i./kg on vegetation and 4.3 mg a.i./kg in soil one hour after application of fipronil at 10-12.5 g a.i./ha (Gadji *et al*., 1997). The project measured fipronil and metabolite residues on vegetation and soil over considerable periods after treatment (see Tables 5-8).

The mean half-life for fipronil degradation was determined as 48 h on millet leaves (during the rainy season), 150 h on dry leaves and in soil and 212 h on grass (arid zone). Two major degradation products were identified - MB46136 (by oxidation and photo-oxidation) and MB46513 (by photolysis) (Gadji *et al*., 1997).

Residue analysis

Fipronil residues have been determined by gas chromatography (GC) with mass spectrometry (MS) and electron capture (EC) detection using an HP-1701 capillary column with a temperature programme of 150-2500C at 100C/min held at 2500C for 16 min. Retention times were 13.95 min for fipronil and 11.55, 13.48, and 13.70 min for the desulfinyl, detrifluoromethylsulfinyl and sulfide derivatives respectively. High pressure liquid chromatography (HPLC) with a reversed phase Ultrasphere C18 column using methanol/water as the mobile phase was used to determine polar metabolites in aqueous fractions from mice faeces (Hainzl & Casida, 1996).

Bobé *et al* also used GC with EC detection based upon an unpublished method provided by Rhône-Poulenc (Bobé *et al*., 1998).

GC with EC failed to produce an interpretable chromatogram for residues less than or equal to 0.002 mg/kg, as did Mass Selective (MS) detection using a Varian Ion Trap Saturn IV. MS/MS detection provided a limit of detection based on quantity injected of less than 10 pg. Linearity of detection was demonstrated for standard solutions between 0.005 and 10 mg/l. Recovery rates ranged from 70-110% (Goller *et al*., 2000). Clean up of vegetation samples for fipronil residue analysis with florisil using solvent elution was found to be ineffective, giving poor recoveries (<30%) of fipronil from spiked samples. Gel permeation chromatography was eventually found to give satisfactory results, especially with grass and leaves containing high levels of chlorophyll and other coloured pigments (King and Aigreau, 2000).

The Locustox project did not describe its residue analytical method due to a confidentiality agreement with Rhône-Poulenc/Aventis, but recovery rates were good (62-110%) (Gadji *et al*., 1997).

Agricultural Impacts

IPM compatibility

There is conflicting evidence over the suitability of fipronil for use in Integrated Pest Management (IPM).

There is conflicting evidence over the suitability of fipronil for use in Integrated Pest Management (IPM), which is generally recognised as a route towards more ecologically sustainable agriculture.

In contrast to toxicity tests under controlled conditions, the assessment of pesticide impacts on natural populations is subject to much greater variation which can lead to differing results. This is due, among other factors, to differences in the local environment, the history (previous applications) of the areas sampled, and to the methodologies (sampling procedures, experimental design) employed. Another major factor is the degree of control the researcher has, particularly in on-farm research.

Field study results range from good selectivity by fipronil for certain beneficial insects and lower toxicity than (the highly toxic) methyl parathion and endosulfan (Hamon *et al*., 1996); through slight and transitory decline in abundance of certain predators and parasitoids and little difference between fipronil and other insecticides (Sparks *et al*., 1997; Tillman & Mulrooney, 1997; Peveling, 2000); to reductions in beneficial arthropods and poorer crop damage prevention than a comparative insecticide (Parker & Huffman, 1997).

The Locustox study concluded that fipronil is relatively toxic to the beneficial invertebrates tested (natural enemies and soil insects) (Everts *et al*., 1998), which implies that its potential for successful use in IPM in agricultural situations similar to those investigated by Locustox in Senegal is low.

High toxicity of fipronil to a number of parasitoids useful in agriculture has been recorded.

High toxicity of fipronil to a number of parasitoids useful in agriculture has been recorded. Field trials in Mauritania with relatively low and moderate doses of fipronil (4.2 and 13.4 g a.i. ha-1, respectively) concluded that at these doses there were adverse impacts on various parasitic and predatory wasps, potentially beneficial to agriculture (Balança & De Visscher, 1995). Following field trials with fipronil at 2 g a.i./ha against Sahelian grasshoppers in Niger there was a slight and transitory decline in abundance of hymenopteran parasitoids (Scelionidae, Braconidae and Trichogrammatidae) (Peveling, 2000a). Some adverse effects of fipronil (4 g a.i./ha) on Ichneumonidae and Chalcidoidea in Siberia have also been shown (Solokov, 2000). Fipronil is relatively highly toxic to the ectoparasite *Catolaccus grandis* [Hymenoptera: Chalcidoidea], a natural enemy of cotton boll weevil (Elzen *et al*., 1999) and *Cotesia marginiventris* [Hymenoptera: Braconidae], a natural enemy of cotton pests (Tillman & Scott, 1997).

Predators beneficial to agricultural production generally seem to show fewer adverse effects from fipronil than do parasitoids.

Predators beneficial to agricultural production generally seem to show fewer adverse effects from fipronil than do parasitoids. For example, fipronil shows low toxicity to the convergent ladybeetle (Kaakeh *et al*., 1996); was toxic to *Doru lineare* [Dermaptera], but showed good selectivity towards the coccinellids *Cycloneda sanguinea* and *Scymnus* sp.; showed no effect on *C. sanguinea, Scymnus* sp. nor *Chrysopa* spp. 5 days after spraying; was non-toxic to *Scymnus* spp. at 50 g a.i./ha, but did cause knock-down of *Ceratocapsus dispersus* and *Orius* spp. with populations recovering 7 days after treatment; did not affect spiders at the same application rate and although some suppression of hemipterous predators was observed, full recovery occurred 10 days after treatment. Predatory coleoptera were reduced by 70% at 5 DAT, but showed gradual recovery (Hamon *et al*., 1996). Fipronil at 64 g a.i./ha and 75 g a.i./ha showed selectivity towards *C. sanguinea*, *Scymnus* sp., *Geocoris* sp., *Nabis* sp., *Doru lineare* and spiders with moderate knockdown and low residual action for 3 days (Hamon *et al*., 1996). *(Authors' note: All this information was provided with no data or methodologies against which to judge validity of claims).* The exception are ground-dwelling predatory beetles which do seem to be generally adversely affected by fipronil, particularly Carabidae (Balança & De Visscher, 1995; 1997b; Danfa *et al*., 1999).

Fipronil is reported to be non-toxic to spiders by Rhone-Poulenc researchers, who stated that even foliar spraying did not reduce populations of these predators (Bostain & Long, 1997). However, results from barrier spraying in grasslands in Madagascar showed evidence that relative abundance of immature spiders was reduced in the short term following application of fipronil (Tingle & McWilliam, 1998; 1999). Subsequent studies in Madagascar have also shown adverse effects of fipronil on spiders (Peveling 2001). Toxicity of fipronil to spiders was reported in field trials in Siberian grasslands, where fipronil caused more severe non-target impacts than chlorpyrifos (Solokov, 2000).

Fipronil also showed more adverse and longer lived impacts than chlorpyrifos in a Locustox project comparison between non-target effects of these two insecticides on epigeal beetles and soil arthropods (Danfa *et al*., 1999).

The finding that fipronil is toxic to both *Beauveria bassiana* and *Metarhizium anisopliae*, two fungi used in biological control of locusts and grasshoppers (Moino & Alves, 1998) suggests that it is unsuitable for use in areas where these mycopesticides have been applied as part of prevetative locust control operations. The indications are that fipronil may be incompatible with locust IPM, hence this possibility requires further urgent investigation.

The Amendment to the Supplemental Environmental Assessment (SEA) to include fipronil stated that "toxicity to certain organisms, including Honeybees may limit its use in and around areas with major honeybee activities" (Belayneh, 1998).

Following field trials in Mauritania with moderate and relatively low doses of fipronil (13.4 and 4.2 g a.i. ha-1, respectively), a study by CIRAD-GERDAT-PRIFAS concluded that at these doses the severe impact of fipronil on predatory and detritivorous beetles could cause deleterious losses of these useful insects if spraying covered large areas. The risk of slowing biogeochemical cycles (notably nitrogen) and decreasing fertility of soil could not be ignored (Balança & De Visscher, 1995).

The ecological implications of the severe and long-lasting impact from fipronil as barrier sprays for locust control in Madagascar on termites (*Coarctotermes* spp.) may be very serious, due to the importance of termites in nutrient cycling, soil structure, water penetration into soils. Termites are a "key-stone" group in the ecology of grassland savannah habitats in Madagascar (Tingle & McWilliam, 1999). Follow up studies have reaffirmed severe adverse effects on termites and demonstrated food chain links to effects on lizards and mammals (Peveling 2001). Locustox studies also found long lasting negative impacts on "beneficial" termites in savannah grasslands and recommended further studies to evaluate ecological impacts (Danfa *et al*., 1999). Termites are also important to the livelihoods of small-scale farmers in the savannah areas of south-western Madagascar. Local people "harvest" termites (especially the queens) from mounds in order to feed their domestic fowl (particularly chickens) (Tingle & McWilliam, 1999; 2000).

> The ecological implications of the severe and long-lasting impact from fipronil ... for locust control in Madagascar on termites may be very serious.

In a comparison of various insecticides, including fipronil for boll weevil (*Anthonomis grandis*) control, the effect on non-target arthropods (pests and beneficials) and impact on cotton production were also examined. The results noted that the Regent (and Vydate) plots contained significantly more beet armyworm damage than any other treatment areas. Regent had the highest percentage reduction of beneficial arthropods however Regent treated plants yielded more damaged bolls than all the other treated plots but, for reasons not understood, had the highest lint production (Parker & Huffman, 1997).

> ... in rice production in Vietnam ... where pesticides had been (previously) heavily used, fipronil had little adverse impact on beneficial organisms ... but where previous pesticide use was low, negative effects of the insecticide were apparent.

Comparative effects of early season applications of azinphos-methyl, oxamyl, two rates of endosulfan, ULV malathion and fipronil on populations of beneficial arthropods in cotton were examined in large-plot field studies in Texas, USA. Few treatment effects could be statistically demonstrated after the first application of insecticides because of generally low population levels of beneficial arthropods and absence of an untreated control. However population trends suggested that applications reduced beneficial arthropod levels temporarily. Analyses of second application results indicated that all insecticides immediately suppressed beneficial insect populations, although population recovery occurred, apparently by immigration. The choice of early-season insecticide appeared to have little influence on the effects of these applications on beneficial arthropod applications. In addition, general disruption of the natural enemy complex in cotton was not achieved in field sized treatment areas because of immigration of beneficial arthropods from surrounding areas (Sparks *et al*., 1997).

The tolerance of two natural enemies, *Geocoris punctipes* and *Cardiochiles negriceps* to residues of malathion, fipronil and cyfluthrin applied ULV was determined for 0, 24, and 48 hours after treatment (HAT). Toxicity to the target pest, *Anthonomus grandis* was also evaluated. Exposure to malathion residues at 0 HAT resulted in highest mortality for the three insects. Cyfluthrin was less toxic than malathion at 0 HAT for all insects. Toxicity of malathion residues decreased sharply at 48 HAT for all three insect species. Toxicity of fipronil remained the same for *A. grandis* from 0 - 24 HAT but was lower for the two natural enemies at 24 HAT than 0 HAT., Fipronil was also less toxic to *C. nigriceps* than to *G. punctipes* at 24 HAT. Fipronil was the only insecticide which had continued toxicity to *A. grandis* at 48 HAT. Toxicity to *A. grandis* was much lower with cyfluthrin than malathion and fipronil at 24 HAT. However, cyfluthrin was more toxic to the two natural enemies than to *A grandis* at 24 HAT (Tillman & Mulrooney, 1997).

Field trials were conducted in 1996 in Arkansas to evaluate the efficacy of several insecticides against the tarnished plant bug (TPB) *Lygus lineolaris*, on cotton plants. Fields in which the trials were conducted had not been sprayed previously that season with insecticides. In a cage bioassay, bug mortality at 96h after application was greater on plots treated with fipronil 2.5 EC (0.068lb/A) than those treated with Karate (lamda cyhalothrin) 1 EC or 2.09 CS (both 0.030lb/A) (Teague & Tugwell, 1997.). *(Authors' note: Data in their results table do not agree with this observation*). All pesticide treatments significantly reduced the number of plant bugs and hemipteran predators compared to the control treatment. It is suggested that the relative susceptibility of the plant bug population was related to absence of selection pressure due to the lack of insecticide application earlier in the season (Teague & Tugwell, 1997).

Plots treated with Regent 2.5EC for plant bug control also harboured generally lower beneficial insect populations than those of plots treated with 3 other insecticides (dimethoate, imidachlorprid and vydate) (Allen *et al*., 1997).

The compatibility of fipronil with IPM of citrus pests in southern Africa is under question, following findings that fipronil is detrimental to predatory mites (Grout *et al*., 1997).

Examination of the effects of fipronil (and other pesticide) use in rice production in Vietnam showed that fipronil reduced predator numbers in the crop and on the paddy water surface in one study, but not in another. The differences were attributed to the degree of previous pesticide use. Where pesticides had been heavily used, fipronil had little adverse impact on beneficial organisms and therefore on the efficacy of IPM, but where previous pesticide use was low, negative effects of the insecticide were apparent. The study concluded that Regent had some disturbing negative impacts on aquatic organisms (Johnsen, 1998).

In a study in rice fields of southern Vietnam (Tien Giang, Mekong delta), with reasonable densities of insects, a major impact of pesticides on population densities was observed.Applications of fipronil in this study were: Regent 0.3G at 20 days after transplanting (DAT), 30 g a.i. ha-^{1} and a Regent 800 WG at 71 DAT, 25.6 g a.i. ha-1.

Assessment of effects was based on the following functional groups:

- Pests: Leaf-eaters (planthoppers[5] , leafhoppers[5] , herbivorous grasshoppers and crickets, some bugs[5], leaf-folders, etc); Stem damagers (mainly stem borers); Root damagers; Grain feeders; Seedling damagers
- Predators: On leaves and stems (ladybird beetles, some carabids and staphylinids, many spiders); On the water surface (spiders of the family Lycosidae, predatory bugs from the families Gerridae and Veliidae); In the water (predatory bugs from the families Corixidae[6], Notonectidae, Belastomatidae, Naucordiae, and beetles from

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[5] NB. These are NOT leaf eaters, but sap-suckers. This is an erroneous classification by the authors).

[6] written as "Coxiridae" in text, but presumably the authors mean Corixidae.

Total Pest populations were significantly reduced in the fipronil treated plots late in the season.

the families Gyrinidae, Hydrophilidae (larvae), Haliplidae (larvae) and Dytiscidae).

- Parasitoids
- Detritivores and filter-feeders (free-swimming mosquito larvae such as Chironomidae and Culicidae)
- 'Neutrals' (some adult Diptera)
- Other organsims sampled were: Zooplankton; Cladocera, Copepoda and Ostracoda; Soil dwelling organisms: Oligochaetae and Chironomideae (different to those in the water) and 'others', e.g. snails.

(Note that in the discussion below, 'Total Pests' are all those groups listed above. 'Total Predators' is the sum of predators, except those in the water.)

Total Pest populations (see above) were significantly reduced in the fipronil treated plots late in the season (after 69 DAT), but before then the differences between plots were negligible. Populations of predators were also reduced, and at an earlier stage (from 38 DAT) and by a greater proportion. Numbers of pests were 50m^{-2} at the start, rising to c 160 in the controls and to c 70 in fipronil plots. Initially populations of predators were greater than prey (100m^{-2}) increased steadily through the season in the control plots (to 300m^{-2}), and declined in the treated (to c 50m^{-2}).

Fipronil seemed more effective in controlling stem-damaging pests than leaf eating ones on the basis of population numbers declining over the season, although there were no significant differences between control and treated for stem damagers. Leaf-eating pests were significantly lower in treated at the end (69 and 72 DAT), i.e. somewhat delayed- 50 days after the first application, the second at 70 DAT had little impact.

All groups of predators were greatly reduced, with very consistent decreasing trend in treated and in contrast increasing numbers in control plots. This applied particularly to predators on the plant and to those on the water surface (Johnsen *et al*, 1997a). A factor in this decline could be the reduction in prey population available rather than direct toxicity of fipronil itself (Bostain & Long, 1997). If insufficient food is available the prey population decreases through migration or starvation. This is supported by the gradual decline in numbers and also by the large pest populations on the control plots supporting a large predator population.

In a second study in the same area (but in different rice fields which had been frequently sprayed with pesticides in the past), fipronil treated fields showed little difference in populations of pest organisms and their predators compared to those of the control fields (Johnson *et al*, 1997b). In these field-based experiments, fipronil was applied twice; at 20 days after sowing (DAS) at a rate of 3 kg[7] a.i. ha^{-1} (as Regent 0.3G), and at 71 DAS at 25.6 g a.i. ha^{-1} (as Regent 800WG).

Although no significant effects were observed, it was noted that insect densities very low in all the treatments- 20-40 m^{-2} for total pest, 5-10 for total predators, similar for all the treatments, including the control. The predator:prey ratio was thus low at c <0.5. This is attributed to a history if heavy pesticide use in this area, together with other changes in farming practices, such as the substitution of organic fertilisers by chemicals (urea). The impacts of pesticides were therefore minimal due to the damage done to the biota by pesticides and other agrochemicals in previous years.

Numbers of aquatic organisms (mosquito larvae and aquatic predators) had population maxima early in the season (21 DAT) and declined thereafter in all treatments, but generally significantly more so in the treated plots. Numbers of predators peaked at 70 m^{-2} (control) and 25 m^{-2} (fipronil); at the end of the season these had fallen to <10 m^{-2} in both.

The predator:prey ratio fluctuated in all plots, with a peak at 21 DAT. Control plots generally had a significantly greater ratio towards the end of the season, in spite of the greater pest population, as predator numbers tripled over this period.

Rice yields at this site differed little between treatments- 3.2 t/ha in the control, 3.3 in treated areas. These were lower than those obtained at Ha Bac (Red River Valley, northern Vietnam, see below) and did not show any benefit of using pesticide, either in controlling pest-induced yield loss or stimulation of growth (see below for more discussion on this).

There was little effect on pest densities or on predators in the rice canopy.

In contrast, there was an immediate and long-lasting (>50 days) impact on aquatic organisms; the predators in the water and mosquito larvae, and similarly for chironomids in the mud. The effects on zooplankon was less clear.

In their rebuttal to the DANIDA report, Bostain & Long (1997) comment that the toxicity to mosquito larvae was not necessarily detrimental, and that Rhône-Poulenc (RP) were looking at this application of fipronil also.

It was reported that farmers used fipronil to control bund-destroying crabs in rice fields, suggesting that it may also be toxic to shrimps (Johnsen,1997 *in litt*., quoting Bostain). This toxicity has been confirmed in other reports (see section on 'Aquatic Organisms'). This poses risks in integrated rice-fish (either in ponds or 'wild') or rice and shrimp-pond farming systems.

... because of the impacts of fipronil on the populations of aquatic organisms, there is likely to be environmental consequences of its use.

The conclusion of the DANIDA reports is that insecticides are not required in rice agriculture, as the natural enemies will keep pests to an acceptably low level, as demonstrated in the control (unsprayed) plots of the trials. Further, because of the impacts of fipronil on the populations of aquatic organisms, there is likely to be environmental consequences of its use. Johnson *et al*, (1997c) cite the risk in areas downstream of the treated fields, such as shrimp farms.

Other (non-insecticidal) effects of Fipronil use in agriculture

Two products, Regent 3 GR and Regent 50 SC, as granular or suspension concentrate formulations, have been specially adapted to Indian rice-growing methods and thoroughly tested in the field. It was claimed that farmers appreciated their persistence in controlling the most commonly-encountered pests and their positive effects on root growth and rice yield (Rhône-Poulenc, 1997).

[7] This is an extremely elevated application rate. We question whether the Table is incorrect and whether 3 kg Regent 0.3 was applied per ha giving an application rate for fipronil of 15-30 g a.i. per ha.

A striking increase in grain yield was observed for the fipronil treated plots...

In their rebuttal to the DANIDA report, Bostain & Long (1997) mention the non-insecticidal aspects of fipronil in increasing yields. There seems to be some plant hormonal effect which encourages the development of the root system, so enabling the plant to better exploit the nutrients available in the soil. The increase in yield was about 12% compared to pest-free controls, so the difference was not due to pest stress.

A striking increase in grain yield was observed for the fipronil treated plots, and for both formulations (Johnsen *et al*, 1997a). The yield for control plots was 4.4 t ha^{-1}; that for fipronil 6.4 t ha^{-1}. The authors (Johnsen *et al*, 1997a) attribute this to micro-nutrients supplied with the insecticide formulation. This was refuted by RP on the basis that the amount of micro-nutrient in the formulation, even if they were based on the analyses presented in the DANIDA report were true, would be too small to have any effect on the yield, and certainly not to the extent observed in this trial. Another rebuttal was that the yield increase was seen for both formulations; the R-800 is a concentrate which is made up in water, so contains no 'filler' (the granular formulation has- 'volcanic sand' (Bostain & Long, 1997). They suggested stimulation of root growth. This may be true, but in this trial the crop was harvested 87 days after planting, and only 16 days after the application of Regent-800WG. It seems unlikely that the increase in yields, which were very similar to Regent-0.3G applied 67 days before harvest, could have arisen from may of the mechanisms suggested by either DANIDA or RP in such a short period. This issue requires further investigation before any conclusion can be drawn.

There was evidence of stronger root system development in the fipronil treated plants.

In the context of rice farming systems, these are very respectable yields, and were considerably greater than those reported for another trial (Tien Giang; 3.1-3.2 t ha^{-1}; Johnson *et al*., 1997b). Yet the soils of Ha Bac are on 'very old agricultural lands' and so are more likely to be deficient in nutrients whereas those at Tien Giang receive fresh sediment each year to maintain fertility. No analyses of the major nutrients (N, P & K) were presented, however, although the data should be available at the respective research stations. Report mentions 'old alluvial clay, low N, P, K and slightly acidic (pH 5.5-6.0)'. Different rice cultivars were used- IR64 at Tien Giang and CR203 at Ha Bac, which may have different yield characteristics and/or different responses to nutrients or to biologically active chemicals. Without account being taken of these factors, cause and effect can not be concluded from these studies.

The severity of dermal reactions in some dogs and cats is of concern.

In response to RP and as a further check of yield increases with fipronil treatment reported by Johnson *et al*. (1997a) the experiment was repeated (Johnson *et al*., 1997c), with the addition of a commercially-available foliar spray fertiliser treatment (N, P, K, and several micro-nutrients). The same fields could not be used as the 1996 (Johnson *et al*, 1997c) experiment, but nearby ones, 50m away. Also, a different variety of rice was used: C70 (CR203 in 1996). Comparability of results is thus open to question.

Where the fields were well fertilised (c 7t manure ha^{-1}, basal application, plus 140-200 kg urea ha^{-1}, the latter applied as an equal split, basal and late at tillering) there were no significant differences- all the yields were 5.0-5.5 t ha. One field had less fertiliser (4 t ha^{-1} manure, 140 kg urea ha^{-1}, same management otherwise). Here there were significant increases in yields for both foliar fertiliser and fipronil- 3t ha^{-1} control, 4t ha^{-1} both treatments, with no significant differences between them.

Johnson *et al*., (1997c) suggest that as fipronil did not increase yields when the input of nutrients was sufficient or was required to control pests, it is not necessary to use it.

There was evidence of stronger root system development in the fipronil treated plants (Stevens *et al*., 1998). At an initial application rate of 12.5 g active ha^{-1}, fipronil levels in the water column declined from 2.1 mg l^{-1} 1 day after sowing to 0.01 mg l^{-1} 14 days after sowing (DAS). At 22 DAS the parent compound was below detection limits (0.005 mg l-1). Four non-replicated commercial scale trials of fipronil were conducted in which three treatments or treatment combinations were evaluated. In general, fipronil (12.5-15.75 g a.i. ha^{-1}) either alone or followed by a post-sowing chlorpyrifos treatment (75 g a.i. ha^{-1}) at 10-15 DAS provided a level of control equivalent to paired chlorpyrifos applications (75 g a.i. ha^{-1} at 2-5 and 10-17 DAS), but at one site fipronil alone was inadequate without a post-sowing chlorpyrifos treatment. This indicates that fipronil applied to seed at 12.5 g active ha^{-1} is a more efficacious seed treatment than malathion at 300 g a.i. ha^{-1} and provides protection against chironomids for 9-14 DAS (Stevens *et al*., 1998). An additional post-sowing insecticide application may still be required in some seasons, but should only be applied in response to high larval populations and evidence of crop damage.

The available data on plant metabolism indicates that, when applied to the leaves at the doses registered or recommended for field use, fipronil undergoes very little, if any, translocation from treated areas (Belayneh, 1998). This is in contrast to Bostain & Long who suggested that fipronil (applied in the granular form) is released into the soil, taken up by the roots, and translocated to the leaves. This systemic action then is a factor in the control of pests and is unavailable to the predators. The product has limited systemic effect in plants but can be fairly persistent on foliage - minimum 3 weeks (FAO, 1997). Although this makes it unavailable to sucking pests, including aphids and jassids, insect pests such as l/g that forage on the whole vegetation can be easily affected by the insecticide.

Effects on domestic animals

There was an increase in the rate of adverse "events" incidents reported from exposure to "Top Spot" in dogs between 1996 and 1998. However, the rate of adverse effects incidents is still very low (USEPA, 1998b).

The severity of dermal reactions in some dogs and cats is of concern. Label revisions to deal with this have been recommended by the USEPA. The Bichon Frise breed is particularly susceptible to adverse reactions to Top Spot (USEPA, 1998b).

Most of the deaths were investigated and the cause attributed to a reason other than fipronil exposure (USEPA, 1998b).

Table 9. Reports of "adverse events" following application of fipronil containing products to domestic animals (USEPA, 1998b).

	Frontline ® spray		**Top Spot ® for cats**		**Top Spot ® for dogs**	
	Cats (10)	**Dogs (8)**	**Cats (101)**	**Dogs**	**Cats**	**Dogs (215)**
Dermal irritation		7	74	-	-	183
Systemic reaction	9	3	27	-	-	32
Death✷	6	3	10	-	-	17

✷If If dermal irritation or systemic reactions were observed prior to death, these were also counted.
Numbers in brackets are the total numbers affected: more than one type of reaction may have been recorded for each animal.

No ill effects from the use of fipronil were recorded from widespread use on domestic animals and pets.

Dogs received fipronil-desulfinyl (MB46513) in the diet in a 28-day study at doses of 0, 27, 80, or 270 ppm. The groups at 80 and 270 ppm were terminated early because of mortality. In the group at 27 ppm, one male had a clonic convulsion. Reduced thymus weights and pale livers were also reported at this dose. As effects occurred at the lowest dose, a NOAEL was not identified.

In a 90-day study of toxicity, fipronil-desulfinyl was administered in the diet to dogs at doses of 0, 3.5, 9.5, or 35 ppm. The clinical findings in one female at 35 ppm (increased salivation, prostration, writhing, tremors, absence of rotular reflex, noisy breathing, dyspnoea) were attributed to arteritis and myocardial necrosis on the basis of microscopic findings; however, they may also have been indicative (at least in part) of neurotoxicity, because another female in this group exhibited excessive barking, aggressiveness, irratability, tremors, and increased salivation. On this basis, the Meeting concluded that the NOAEL was 9.5 ppm, equal to 0.29 mg/kg bw per day (WHO/FAO, 1997).

... during 1996 fipronil-containing sprays were the subject of 59 reports of ocular, skin, respiratory, gastrointestinal or other systemic reactions in humans. Most were minor and rapidly reversible ...

Veterinary risks

No ill effects from the use of fipronil were recorded from widespread use on domestic animals and pets (Postal *et al*., 1995; Atwell, Postal *et al*., 1996; Atwell, Sillar *et al*., 1996; Cooper & Penaliggon, 1996; Cochet *et al*., 1997; Harvey *et al*., 1997; Song, 1997; Penaliggon, 1997; Chadwick, 1997; Jacklin, 1997; Araujo *et al*., 1998; Beck & Wrieg, 1998; Cutler, 1998; Hutchinson *et al*., 1998; Franc & Cadiergues, 1998; Nuttall *et al*., 1998; Bordeau, 1998; Beck, 1999b; Davey *et al*., 1999; Hugnet *et al*., 1999; Estrada-Pena & Ascher, 1999).

However, the manufacturers do not recommend the use of fipronil (Frontline Spray) on rabbits and they have revised their product data sheet accordingly (Cooper & Penaliggon, 1997).

[14C] fipronil was topically applied to the interscapular region of a Beagle (dog) at a dose of 12 mg/kg. Using autohistography, the radiography was detected in the skin and appendages at various intervals after application. Reactivity was mainly seen in the stratum corneum, the viable epidermis and in the pilo-sebaceous units (mainly sebaceous glands and epithelial layers). [14C] fipronil was detected up to 56 days after treatment in the application area (neck) and in the lumbar zone. No radioactivity was detected in the dermal or hypodermal layers, confirming the low percutaneous passage of fipronil (Cochet *et al*., 1997).

Fipronil has been classified as a Group C (Possible Human) Carcinogen by the USEPA ...

Human health impacts

There are no known studies undertaken with human subjects, although human cells have been used in some carcinogenic studies. A cytogenic assay using human lymphocytes and 98.7% pure metabolite showed no evidence of clastogenic effects. Fipronil is reported to bind strongly to skin, and does not come off when it is dry (USEPA, 1998).

Fipronil seems to enhance the hepatic metabolism and excretion of thyroid hormone, and it was noted that,"more information was needed to identify other potential antithyroid modes of thyroid carcinogenic action".

The Appraisal Panel for Human Suspected Adverse Reactions to Veterinary Medicines reported that during 1996 fipronil-containing sprays were the subject of 59 reports of ocular, skin, respiratory, gastrointestinal or other systemic reactions. Most were minor and rapidly reversible but amendments were recommended to the product literature to minimise operator exposure (ACP, 1999).

The risk of acute toxicity to people from the use of fipronil for locust control is considered as negligible, even if dead locusts are consumed directly (as certainly can happen in Madagascar (Warburton, 1994)). Based on the NOEL for subchronic toxicity in dogs of 0.5 mg/kg bodyweight and a "safety factor" of 100 in translating risk to humans, the acceptable NOEL for humans (including both men, women and children) would be 0.005 mg/kg. This would mean that a person of 60 kg could safely take in 0.3 mg/day. If one locust contains 0.0006-0.001 mg fipronil, the person could eat 300-500 insects per day over a prolonged period without adverse effects (Everts, 2000 *in litt*.).

The NYS, Division of Solid and Hazardous Materials concluded in 1996, that a formulation called Frontline Spray Treatment would not be registered at that time. This was because of the possible health risk to workers in the pet industry, especially to those people involved in dog-grooming, based upon a risk analysis from a number of parameters involving daily use (New York State Department of Environment & Conservation, 1996).

Fipronil has been classified as a Group C (Possible Human) Carcinogen by the USEPA based on an increase in thyroid follicular cell tumours in both sexes of the rat. The increase is statistically significant by both pair-wise and trend analyses. The RfD methodology was selected for

... the Pesticide Registration authorities in the UK do not consider that there is a risk of carcinogenic effects of fipronil to humans.

quantification because the thyroid tumours appeared to be related to a disruption in the thyroid-pituitary status and there was no apparent concern for mutagenicity or available information from structurally related analogues (USEPA, 1996).

However, the Pesticide Registration authorities in the UK do not consider that there is a risk of carcinogenic effects of fipronil to humans. This is due to evidence that fipronil has an indirect effect in inducing cancer in the rat thyroid gland, acting via increased hepatic clearance of thyroxine (T_4) (ACP, 1999). There are 2 basic mechanisms whereby chemicals may induce thyroid gland neoplasia in rodents; one through a direct carcinogenic effect on the thyroid itself; the other through a variety of mechanisms which disrupt thyroid function and produce neoplasia in the thyroid gland secondary to hormone imbalance (McClain, 1992). Fipronil seems to act via the second mechanism (USEPA, 1998; ACP, 1999). There are important differences in thyroid gland physiology between rodents and humans, which mean that the rat may not be a good model for thyroid carcinogenic mechanisms in humans (Hill *et al*., 1989; McClain, 1992).

The decision on which standard to accept or which criteria to use in assessing risk to humans is a political one. The USEPA and British ACP decisions above were based on the same data (Everts, 2000 *in litt*.).

Acceptable Daily Intake (ADI)

A World Bank Expert Panel recommended against the use of fipronil on crops for locust control in Madagascar, until ADIs had been set (World Bank, 1998).

The acceptable daily intake (ADI) proposed by Rhône-Poulenc was 0.00025 mg/kg bw/day. While some countries such as Brazil have accepted this level, others, including Australia, France and Japan have established 0.0002 mg/kg bw/day as the ADI.

The meeting of the FAO and WHO joint panel of experts established an ADI of 0-0.0002 mg/kg body weight (bw) on the basis of the NOAEL of 0.019 mg/kg bw per day in a two-year study of toxicity and carcinogenicity in rats and incorporating a safety factor of 100 (FAO, 1998).

The FAO/WHO meeting also considered that a separate ADI should be established for fipronil disulfinyl on the basis that it could be a significant residue and that its toxicity is greater than that of the parent molecule. The temporary ADI for desulfinyl has been set at 0.00003 mg/kg bw/day (FAO, 1998) and is expected to be published in the Codex Alimentarius by the year 2000 (Belayneh, 1998).

The acceptable daily intake (ADI) for fipronil is 0.0002 - 0.00025 mg/kg bw/day.

Acute toxic effects in humans

Unknown at present.

Poisoning reports

None found in the literature available to date.

Non-target impacts on Wildlife

Effects on Aquatic Organisms

Fipronil varies from being highly toxic to very highly toxic to many aquatic organisms, when calculated on the basis of exposure to relatively low concentrations of the active ingredient under controlled laboratory conditions. The risk of these concentrations being reached in the field, however, is very low under recommended conditions of usage (dosage rates, methods of application). Fipronil is not harmful under natural conditions but, because of slow rate of dissipation fipronil may show chronic effects to aquatic organisms and further studies on chronic toxicity are needed to adequately assess the risks.

There is little information of toxicity to aquatic organisms directly attributable to fipronil in the natural environment, as there have been comparatively few detailed field surveys made on this. Under field conditions, fipronil is known to adsorb to soil particles and has low solubility in water, suggesting decreased potential for toxicity for aquatic organisms. It is not known to enter aquatic habitats through leaching. The only major established way of entry to aquatic habitat is through direct application.

A simulation model study conducted by EPA found that run off may be possible from in-furrow treatments (USEPA, 1996).

Fipronil is classified by the FAO's Locust Pesticide Referee Group (LPRG) as low risk to aquatic invertebrates when applied at the recommended dose rate for both barrier and blanket treatments for the control of locusts (LPRG, 1999).

Fipronil is non-toxic to aquatic plants and to algae (USEPA, 1996).

Based on an acute toxicity study on *Daphnia* using fipronil, and three supplemental studies using its metabolites, fipronil was characterised as highly toxic to aquatic invertebrates (USEPA, 1996). Fipronil had an EC50 of 190 ppb for *Daphnia*. An invertebrate life cycle study of *Daphnia* showed that fipronil affects the length of daphnids at concentrations greater than 9.8 ppb. The LOEC was 20 ppb and the maximum allowable toxicant concentration (MATC) was determined as 14 ppb (USEPA, 1996). Metabolites MB 46136 and MB 45950 were more toxic than the parent to freshwater invertebrates (MB 46136 is 6.6 times more toxic and MB 45950 is 1.9 times more toxic to freshwater invertebrates (USEPA, 1996).

Acute toxicity studies (USEPA, 1996) on estuarine animals (oysters, mysids, and sheepshead minnows) shows that fipronil is highly acutely toxic to oysters (EC_{50} of 0.77 ppm) and sheepshead minnows (EC of 0.13 ppm), and very highly toxic to mysids (EC_{50} of 140 pptr). A life cycle study in mysids shows fipronil affects reproduction, survival and growth at concentrations less than 5 pptr. The following toxicity parameters were determined: LOEC = 5 pptr; NOEC < 5.0 pptr, and MATC < 5 pptr (USEPA, 1996).

Toxicity of fipronil to fourth- instar larvae of six

Table 10. Summary of toxicity data for Fipronil on non-target aquatic organisms[8] .

Organism	Toxicity : (LC_{50} unless stated otherwise), [duration of test (h)]	Notes	Ref
Invertebrates			
oysters	0.77 ppm	'highly toxic'	4
Mysid shrimp	140 ppt (trillion)	'very highly toxic'	4
Streptocephalus sudanicus	(EC_{50}[9]) 67.2 (±18.5); [24h]		1
(fairy shrimp)	9.95 (±0.37) mg/l [48h]		
Anisops sardeus (backswimmer)	20.6 (±5.4) [48h]; 9.25 (±2.43) mg/l [24h]		1
Daphnia magna (daphnia)	L(E)C_{50}; 190mg/l [48h]	Standard test org.	3
Daphnia (daphnia)	190 ppt (trillion)*	'highly toxic'	4
Mosquito larvae:			
Aedes aegypti	0.02~0.004 ppm [48h]		5
Ae. albopicatus	0.023 ppm [48h]		5
Ae. taeniorhynchus	0.00043 ppm [48h]		5
Anopheles quadrimaculatus	0.02~0.004 ppm [48h]		5
Culex nigripalpus	0.02~0.004 ppm [48h]		5
Cx. quinquefasciatus	0.02~0.004 ppm [48h]		5
Chironomid midges:			
Chironomus crassicordatus	0.00042 ppm [48h]	Field material	5
Ch. tepperi	LC_{50}: 0.43 ug/L		6
Ch. tepperi	LC_{90}: 1.05 ug/L		6
Glyptotendipes paripes	0.00042 ppm [48h]	Field material	5
Fish			
Oreochromis niloticus	147 (153-212) [24h] - 86 (59-121) [48h] 61 (43-85) [72h] - 42 (29-60) mg/l [96h]		2
Salmo gairdneri	LC_{50}, 248mg/l [96h]	Standard test org.	3
Bluegill sunfish	0.083 ppm [96h]	'very highly toxic'	4
Rainbow trout	0.246 ppm [96h]	'highly toxic'	4
Sheepshead minnow	0.13 ppm	'highly toxic'	4
Birds (aquatic)			
Mallard	NOEC: 1,000 ppm		4
Algae			
Diatom, fresh-water	>0.12 ppm		4
Green algae	>0.14 ppm		4
Diatom, marine	>0.14 ppm		4
Cyanobacteria	>0.17 ppm		4
Higher plants			
Lemna (duckweed)	>0.10 ppm		4

species of mosquitoes (*Aedes aegypti*, *Ae. albopictus, Ae. taeniorhynchus, Anopheles quadrimaculatus, Culex nigripalpus,* and *Cx. quinquefasciatus*) and two species of field-collected chironomid midges (*Chironomus crassicaudatus* and *Glyptotendipes paripes*) was evaluated in the laboratory (Ali *et al*, 1998). All mosquito species were highly susceptible with 48-h median lethal concentration (LC_{50}) values ranging from 0.00043 ppm (*Ae. taeniorhynchus* and *An. Quadrimaculatus*) to 0.023 ppm (*Ae. albopictus*). Chironomus crassicaudatus and G. paripes were also were extremely susceptible (48-h LC_{50} of both species: 0.00042 ppm) to fipronil. Larval mortality checks of *Ae. taeniorhynchus, Cx. nigripalpus,* and *G. paripes* at 24 h and again at 48 h revealed delayed activity of this compound against these species. First-instar larvae of *Ae. albopictus* and *Cx. quinquefasciatus* were significantly (P < 0.01) more susceptible to fipronil than the fourth -instar larvae of these mosquito species.

Fipronil was bioassayed against final instar larvae of *Chironomus tepperi* Skuse, and found to be highly toxic (LC_{50} 0.43 mg l-1, LC_{90} 1.05 mg l^{-1} relative to conventional organophosphorus insecticides (Stevens *et al*. 1998).

The toxicity of fipronil (and eight other insecticides) used in the control of Desert Locust to two aquatic organisms *Streptocephalus sudanicus* (Branchipoda, Anostraca; fairy shrimp) and *Anisops sardeus* (Hemiptera, Notonectidae; backswimmer) was tested under controlled conditions. These are important organisms in temporary ponds in Senegal. The authors (Lahr *et al*, 1998) considered the incorporation of data on indigenous species as a requirement in making balanced risk assessments in semi-arid regions, especially temporary ponds. This has also been emphasised by Everts (1997) and Lahr (1997).

The toxicity of fipronil to the indigenous species

Fipronil varies from ... highly toxic to very highly toxic to many aquatic organisms ... at relatively low concentrations...The risk of these concentrations being reached in the field, however, is very low under recommended conditions of usage.

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[8] References for Table: 1. Lahr *et al*., 1998 2. Diallo *et al*., 1998 3. Thomlin, 1994 4. USEPA, 1996 5. Ali *et al*., 1998 6. Stevens *et al*., 1998 7. Bostain & Long, 1997

[9] EC_{50} was used for S. sudanicans, as they displayed a more complex pattern of reactions- immobilisation, debilitation, and death.

* Duration of test not supplied

reported here (Lahr *et al*. 1998) was consistently greater than to the standard test species in a pairwise (by species) correlation, generally by an order of magnitude. The data, however, were based on correlation of all eight insecticides where only one combination (*A. sardeus vs S. gairdneri*) was significant ($p<0.05$), i.e. all eight were more toxic. There was no reciprocal pairwise (by pesticide) comparison. The authors conclude that the methods devised for acute toxicity tests gave satisfactory (consistent and reproducible) results and, being simple to perform with basic equipment, are suitable tools for screening the toxicity of insecticides in the Sahel region. Using standard species would, in their opinion, be fruitless, as there was a significant correlation in only one combination (see above); i.e. the standard species do not predict the toxicity of a range of insecticides to the indigenous organisms.

The toxicity of fipronil to ... indigenous species was consistently greater than to the standard test species ... generally by an order of magnitude.

Fish are also a significant part of the biota of these temporary ponds which are also likely to be affected by pesticides (see Table 10) in the locust control programme. *Oreochromis niloticus* (ex *Tilapia*) is a local fish species which found in the freshwaters of inter-tropical Africa. A large part of this area (the range of this species) is within the locust control region (Diallo *et al*, 1998). *Oreochromis* is an important economic species making up a large proportion of the wild catch. It is also used in aquaculture for human food production.

There was no correlation with the toxicity of the eight insecticides between *O. niloticus* vs *S. gairdneri*. Some of this may be due to the test conditions as well as to the organisms themselves. The conclusion that local species need to be used as toxicity test organisms was also emphasised by the authors, supporting the findings of Lahr *et al* (1998).

Fipronil is very highly toxic to bluegill sunfish (LC$_{50}$ of 0.083 ppm) and highly toxic to rainbow trout (LC$_{50}$ of 0.246 ppm) and sheepshead minnows (EC$_{50}$ = 0.13 ppm) on an acute basis (USEPA, 1996). It is also highly toxic to Japanese Carp (LC$_{50}$ (96 h) 0.34 mg/l (Colliot *et al*., 1992). The results of a fish early life-stage toxicity study in rainbow trout show that fipronil affects larval growth with a NOEC of 0.0066 ppm and an LOEC of 0.015 ppm. The metabolite MB 46136 was more toxic than the parent compound to freshwater fish (6.3 times more toxic to rainbow trout and 3.3 times more toxic to bluegill sunfish) (USEPA,1996).

Fipronil is very highly toxic to bluegill sunfish ... and highly toxic to rainbow trout ...

A number of assumptions are required in risk analysis. The principle of the calculation of the risk to fish and aquatic invertebrates is based on FAO rates of application (the dosage, as g a.i./ha) and the concentration this would reach in an area of water (Canton *et al*. 1991). A depth of 25cm was used by the authors (Diallo *et al*. 1998). On this basis the estimation of contamination by fipronil was 'small' [as were the 5 of the others; Bendiocarb- 'potential'; Diflubenzuron 'negligible']. In the case of fipronil, this was due to the low application rate (6.25 g a.i./h; FAO, 1996), thus the concentration in water 25cm deep would be 2.5mg/L. The LC$_{50}$ at 96h for *O. niloticus* was 42 mg/L, a ratio (concentration in water/LC$_{50}$) of 0.056; a 'potential' risk is assumed when the ratio reaches 1.0.

Plants

The data for aquatic plants is summarised in Table 10. Fipronil is 'non-toxic' to aquatic plants and algae (USEPA, 1996).

Effects on Terrestrial Organisms

Effects on plants

Fipronil used to coat the seeds of winter leeks was found to cause no phytotoxicity (Ester *et al*., 1997). Fipronil also showed no phytotoxicity to winter rape in Poland (Seta *et al*., 1997).

Continuous exposure of seeds of rice to fipronil at 2000 mg/l for 4 days significantly impaired germination. When exposure was restricted to a 1 h period 48 h after initiation of germination, early post-germination growth was also impaired. Shoot and root development from seeds exposed continuously for 2 days to fipronil, and growth parameters of germinated seeds treated with fipronil for 1 h immediately prior to sowing showed no evidence of effects. Neither was any evidence of a phytostimulatory effect of fipronil detected (Stevens *et al*., 1999).

Effects on micro-organisms

Fipronil is not known to be toxic to soil microorganisms (USEPA, 1996).

In laboratory toxicity tests fipronil was found to be toxic to both *Beauveria bassiana* and *Metarhizium anisopliae*, two fungi used in biological control of locusts and grasshoppers (Moino & Alves, 1998) - see **IPM Compatability**.

Effects on invertebrates

Fipronil is non-toxic to earthworms (Hamon *et al*., 1996, USEPA, 1996).

Fipronil (Adonis 8.5 UL - 8.5 g/L ULV formulation) is undergoing evaluation for registration in Australia as an insecticide for locust control as an alternative to fenitrothion. The general conclusion from these studies is that fipronil appears to have minimal effect on non-target arthropods (Spurgin 2000; APLC, 2000). *(Authors' note: No data are presented against which to assess the validity of this conclusion).*

Fipronil was found to be toxic to predatory mites (*Euseius addoensis*) in laboratory tests (Grout *et al*., 1997) and there are indications from some field trials that it may have adverse effects on some spiders (Tingle & McWilliam, 1999; Solokov, 2000).

Severe and long lasting impacts of fipronil on a variety of non-target invertebrates were reported after field trials with fipronil at 13.4 g a.i./ha and 4.2 g a.i./ha in Mauritania. There were also indications of similar impacts at a lower dose (3.6 g a.i./ha). Crickets (which may be pests of locally grown crops) were eliminated and did not show any recovery within a month at all three doses. Predatory ground beetles [Carabidae] showed 99% mortality (or more) at the first 2 doses and 81% mortality at the lowest dose, but showed

> In laboratory toxicity tests with 2 species of darkling beetles ... a provisional hazard ranking put fipronil as the most hazardous of 6 conventional insecticides used in locust control.

some recovery at the lower doses during the fortnight following spraying. Detritivorous darkling beetles [Tenebrionidae] also showed over 99% mortality at the higher doses and 85% mortality at the lowest dose, with little sign of recovery at the highest dose but some recovery after 1-2 weeks at the lower two doses. Flies [Diptera] showed no evidence of adverse effects, and there were some indications that certain wasps may have been affected to a small degree (Balança & De Visscher, 1995; 1997b).

Very low doses of fipronil (0.6-2 g a.i./ha) also caused reductions in relative abundance of beetles and wasps and evidence of impacts on flies were also detected. The authors conclude that even at these doses fipronil causes significant adverse impacts on these groups (including some beneficials), comparable with those found using other insecticides commonly used in locust and grasshopper control (Balança & De Visscher, 1997a).

In laboratory toxicity tests with 2 species of darkling beetles which are prominent components of hot arid and semi-arid ecosystems and important locust natural enemies, *Pimelia senegalensis* and *Trachyderma hispida* [Coleoptera: Tenebrionidae], a provisional hazard ranking put fipronil as the most hazardous of 6 conventional insecticides used in locust control. Topical 96 h ED$_{50}$ was 0.1 mg a.i./g body weight and dietary 96 h ED$_{50}$ was 0.22 mg a.i./kg millet bran for *T. hispida* (van der Valk *et al*., 1998).

In laboratory toxicity tests with the parasitoid *Bracon hebetor* [Hymenoptera: Braconidae] the LC$_{50}$ (24 h) was 0.09 ng/cm^2, the highest acute toxicity of the 7 insecticides tested. It also appeared to reduce the longevity and fecundity of female braconids and the authors concluded that "long term effects on reproduction are to be forseen with fipronil". The study gave fipronil the second highest Risk Quotient (RQ) of 7 insecticides tested (based on the relationship between the LC$_{50}$ and the level of residues in millet) (Danfa *et al*., 1998).

The Locustox studies concluded that fipronil is relatively toxic to the beneficial invertebrates tested (natural enemies and soil insects) (Everts *et al*., 1998).

Studies of the non-target impact from emergency applications of fipronil (Adonis 7,5) as barrier sprays for locust control in Madagascar showed adverse impacts of fipronil on termites (*Coarctotermes* spp.), which appears to be very severe. All termite colonies in areas receiving direct spray seem to be adversely affected and the majority ceased activity completely over a number of months, with little recovery seen over a 10 month period.

> Adverse and long lasting effects of fipronil on non-target termites were ... reported in Senegal ... and Madagascar.

Other than the severe impact on termites, it appears that when barrier sprayed, fipronil is generally less harmful in the short-term to non-target terrestrial invertebrates than is the IGR triflumuron. The effects of both IGRs and fipronil on termites and spiders require further detailed investigation. This has now been started and cover-sprays of fipronil are shown to have wider ranging adverse effects on non-target organisms than deltamethrin (Peveling 2001). Fipronil showed adverse impacts only for non-target grasshoppers, immature spiders, Diptera, braconid wasps and possibly bees. None of these effects were particularly severe in the short term. There were also indications of adverse impacts on certain epigeal beetles (particularly Tenebrionidae) and effects on some ground dwelling spiders and crickets could not be discounted (Tingle & McWilliam, 1999; 2001). It was concluded that barrier spraying may have reduced adverse effects of fipronil on some of the invertebrates previously shown to be sensitive to this insecticide (Tingle & McWilliam, 1999).

Adverse and long lasting effects of fipronil on non-target termites were also reported in Senegal (Danfa *et al*., 1999). No significant changes in relative abundance of termites was seen during the first 5 weeks following spraying, but thereafter a statistically significant decline was shown which lasted for at least 2 years. A number of mound building species were involved (*Microcerotermes* sp., *Odontotermes nilensis* [Termitidae], *Psammotermes hybostoma* [Rhinotermitidae]), but long-term adverse impacts were only demonstrated for the beneficial rhinotermitid *P. hybostoma*. This study also demonstrated adverse and long-lived effects on ants (*Monomorium* sp. and *Lepisiota* sp.). Effects on beetles were also consistent with those of a number of other studies, with Tenebrionidae, Carabidae, Histeridae, Curculionidae and Elateridae all showing evidence of adverse impacts from fipronil in the short term. In fact, the only group of beetles included in the study, which did not seem to be affected, was the Scarabaeidae (Danfa *et al*., 1999).

Following field trials with fipronil at 2 g a.i./ha against Sahelian grasshoppers in Niger there was a slight and transitory decline in abundance of hymenopteran parasitoids (Scelionidae, Braconidae and Trichogrammatidae). Ants and two species of herbivorous beetles (*Europe rubra* [Chrysomelidae] and *Dereodus marginellus* [Curculionidae]) showed 80-100% reductions in relative abundance after spraying, with no recovery within a 7 week post-spray period (Peveling, 2000a).

A comparison of non-target impacts from the use of fipronil and chlorpyrifos for control of grasshoppers in pasture and crops of *Bromopsis inermis* in Siberia showed that fipronil (4 g a.i./ha) was found to be more toxic than chlorpyrifos (205 g a.i./ha) to: Acrididae, Lygaeidae, Carabidae, Cicadellidae (from pitfall traps); Acrididae, Lygaeidae, Miridae, Chrysomelidae, Muscidae, Pyralidae and Ichneumonidae (from sweep net catches). Fipronil was equally toxic, with chlorpyrifos to: Araneae, Cydnidae (pitfalls); Araneae and Chalcidoidea (sweep nets). Generally, fipronil caused more severe non-target impacts than chlorpyrifos (Solokov, 2000). A similar conclusion was reached in a Locustox project study on epigeal beetles and soil arthropods (Danfa *et al*., 1999).

Laboratory studies showed that fipronil has low-moderate toxicity to *Hippodamia convergens* [Coleoptera: Coccinellidae], *Chrysopa* spp. [Neuroptera: Chrysopidae] and *Apanteles flavipes* [Hymenoptera: Braconidae]. It is also apparently toxic to *Trichogramma pretiosum* [Hymenoptera: Chalcidoidea] in the laboratory, but very low toxicity was observed in the field (Hamon *et al*.,

> Fipronil is toxic to bees and should not be applied to vegetation when bees are foraging.

1996). *(Authors' note: Neither data nor methods were supplied to evaluate these claims).* However, low toxicity to the convergent ladybeetle was confirmed in lab studies elsewhere (Kaakeh *et al*., 1996) - see **IPM compatibility**. Relatively high toxicity of fipronil to the ectoparasite *Catolaccus grandis* [Hymenoptera: Chalcidoidea], a natural enemy of cotton boll weevil, was detected (Elzen *et al*., 1999). Fipronil is also extremely toxic to *Cotesia marginiventris* [Hymenoptera: Braconidae], a natural enemy of cotton pests (Tillman & Scott, 1997).

Fipronil was found to be toxic to *Doru lineare* [Dermaptera], but showed good selectivity towards the coccinellids *Cycloneda sanguinea* and *Scymnus* sp. by comparison with methyl parathion and endosulfan. In field trials in Columbia fipronil was of moderate to low toxicity to beneficial insects, with no effect observed on *C. sanguinea, Scymnus* sp. nor *Chrysopa* spp. 5 days after spraying. In Peru, fipronil @ 50 g a.i./ha was non-toxic to Scymnus spp, but did cause knock-down of *Ceratocapsus dispersus* and *Orius* spp; however, populations recovered by 7 days after treatment (DAT). (Hamon *et al*., 1996)

Also in Peru in 1995, Regent @ 50 g. a.i./ha did not affect parasitic Diptera, Hymenoptera or spiders. Some suppression of hemipterous predators was observed, but full recovery occurred 10 days after treatment. Predatory coleoptera were reduced by 70% at 5 DAT, but showed gradual recovery. (Hamon *et al*., 1996)

In field trials in Brazil, Regent @64 g a.i./ha and 75 g a.i./ha showed selectivity towards *C. sanguinea, Scymnus* sp., *Geocoris* sp., *Nabis* sp., *Doru lineare* and spiders with moderate knockdown 1 DAT and low residual action 3 DAT. Fipronil was significantly less toxic than methyl parathion and endosulfan (Hamon *et al*., 1996). *(Authors' note: All this information from Hamon et al was provided with no data or methodologies against which to judge validity of claims).*

> ... fipronil could be considered to be highly or very highly toxic to (the lizard) *A. dumerili* ...

The tolerance of *Geocoris punctipes* and *Cardiochiles negriceps* to residues of fipronil applied ULV was determined. The toxicity of fipronil was lower for the two natural enemies at 24 HAT than 0 HAT. Also, fipronil was less toxic to *C. nigriceps* than to *G. punctipes* at 24 HAT (Tillman & Mulrooney, 1997).

Table 11. Acute toxicity of fipronil to selected avian species for which data are available (Hamon *et al*., 1996).

Species	Study	Effect & Levels
Northern bobwhite quail (*Colinus virginianus*)	Acute LD_{50} Sub-acute LC_{50}	LD_{50} = 11.3 mg/kg LC_{50} = 48 ppm NOEC = 19.5 ppm
Ring-necked Pheasant *(Phasianus colchicus)*	Acute LD_{50}	LD_{50} = 31 mg/kg
Red-legged partridge (*Alectoris rufa*)	Acute LD_{50}	LD_{50} = 34 mg/kg NOEL = 16 mg/kg
Field sparrow (*Spizella pusilla*)	Acute LD_{50}	LD_{50} = 1120 mg/kg
Pigeon (*Columba livia*)	Acute LD_{50}	LD_{50} > 2000 mg/kg
Mallard duck (*Anas platyrhynchos*)	Acute LD_{50} Sub-acute LC_{50}	LD_{50} > 2150 mg/kg LC_{50} > 5000 ppm NOEC = 1250 ppm

Key: LD = lethal dose; LC = lethal concentration; NOEC = No effect concentration; NOEL = No effect level.

Fipronil is toxic to bees and should not be applied to vegetation when bees are foraging (Hamon *et al*., 1996). LD_{50} 0.004 mg/bee (Rhone-Poulenc, 1995).

Birds, mammals and other vertebrates

Lizards

Very little work has been carried out on the impact of fipronil on Amphibia and reptiles, even in the laboratory. The only field study appears to be the one carried out in Madagascar. Further studies are required in order to be able to adequately assess non-target impacts on this group. However, the evidence to date points to possible adverse effects of fipronil on lizards.

The LD_{50} of fipronil for the lizard *Acanthodactylus dumerili* [Lacertidae] has been estimated at 30 mg a.i./g body weight in laboratory tests. Surviving lizards did not fully recover until 4 weeks post-exposure. Locomotor activity, prey consumption and body weight remained significantly lower than in the control group and mortality gradually increased during the weeks after treatment (Peveling, 2000b).

In the laboratory, 50% of lizards *Acanthodactylus dumerili* ingesting 30 mg g^{-1} in injected flies died between 3-26 (mean = 17.5) days later. In survivors, overall activity was depressed for 12 days, feeding activity for 14 days (returning to the level of controls after 21 days), and food consumption was reduced for 3 and 4 weeks in females and males, respectively. Body weight declined to 75% of norm for 14 days, remaining lower than normal for 28 days, and liver weight decreased in lizards whether fully dosed or not. In females, liver weight was a mean of 1.6% of body weight, compared to 5.8% in controls. Survivors had still not fully recovered after 28 days, and fipronil could be considered to be highly or very highly toxic to *A. dumerili* on respectively an acute oral or sub-acute dietary basis, and only the latter need now be tested over a longer time period (Peveling & Demba, 1997).

The indications of an effect of fipronil on the lizard *Mabuya elegans* from field studies of non-target impacts of fipronil (Adonis 7,5) barrier sprayed for emergency locust control in Madagascar are consistent with findings of toxicity to lizards from the FAO Locustox project (Everts, *in litt.* 1997). The effect of fipronil appears to be minor and short-lived, but deserves to be followed up to assess the extent and implications of this (Tingle & McWilliam, 1999). Follow up studies in Madagascar have confirmed adverse effects of fipronil on *M. elegans* and *Chalarodon madagascariensis* probably via the food chain link to termites (Peveling 2001).

Birds

Acute toxicity of fipronil has been extensively studied in a number of avian species, and it has been shown that Gallinaceous birds (pheasants, partridges, quail) show a higher sensitivity to

...one of the metabolites of fipronil (MB 46136) is more toxic than the parent compound ... being very highly toxic to Gallinaceous birds and moderately toxic to waterfowl ...

fipronil than passerines (sparrows, warblers and most other small birds) and waterfowl (ducks, geese), which show virtually no sensitivity (Hamon *et al*., 1996) - see Table 11.

It was found that one of the metabolites of fipronil (MB 46136)(see also below) is more toxic than the parent pesticide to the avian species tested, being very highly toxic to Gallinaceous birds and moderately toxic to waterfowl on an acute oral basis. (USEPA, 1996).

In chronic avian reproductive studies, birds show no effects of fipronil at the highest levels when tested against mallard (NOEC = 1000 ppm) or quail (NOEC = 10 ppm).

Experiments conducted on wild caught male red-winged blackbirds (*Agelaius phoenicus*), male and female brown-headed cowbirds (*Molothrus ater*) and female boat-tailed grackles (*Quiscalus major*), which were held for three months in captivity prior to testing were fed with rice treated with fipronil at 0, 325 and 500 mg kg^{-1}. Videotaped observations of test birds revealed no evidence of ill effects, and the birds appeared indifferent to the presence of the fipronil treated seed. In flight pen trials, there was a preference shown for non-fipronil treated seed, and it was found that during feeding, the birds removed 10-20% of the fipronil originally present in the seed when they remove the "hull". The study found no indication that fipronil applied to rice seeds affected the birds' response to the seed. The concentration at which fipronil affects feeding behaviour of birds is not presently known (Avery *et al*., 1998).

There have been relatively few observations on the effects of fipronil on birds in the field, either in the tropics or in temperate areas. In a study on fipronil by PRIFAS (Rhone-Poulenc, 1995), two experiments were carried out, one using 11.04g a.i./ha and a second using 4.20g a.i./ha. An index of abundance and activity by birds in the site treated with 11.04g a.i./ha of fipronil shows the following (see Table 12):

Table 12.
An index of abundance and activity of birds at a site treated with 11.04g a.i./ha of fipronil in Mauritania, November 1994 (Rhone-Poulenc, 1995)

Name	1st count (pre treatment)	2nd count (post treatment)
Falco tinnunculus	2	2
Streptopelia senegalensis	0	1
Urocolius macrourus	1	19
Eremopterix nigriceps	1	3
Galerida cristata	0	1
Oenanthe oenanthe	1	1
Spiloptila clamans	1	0
Sylvia melanocephala	1	4
Sylvia cantillans	1	1
Phylloscopus collybita	1	2
Turdoides fulvus	0	1
Lanius excubitor elegans	1	0
Passer luteus	29	67

- There were no negative effects of fipronil evident on birds, many of whom were breeding.
- The absence of any lethal effects was not surprising because of the relatively low toxicity of fipronil to birds, when compared with certain organophosphates.
- The absence of any indirect effect caused by food deprivation was surprising taking into account the quantities of insects which had been killed.
- The authors concluded that further observations were needed to confirm these results.

No comments were made on the differences in abundance between species before and after the spraying had taken place, although Table 13 showed that 8 out of 14 species had increased in number after 10 days, 2 had decreased, while 4 remained the same. The number of birds sampled was small and the period over which observations were made was also short. (Authors' note: *The conclusions above must be seen in this light).*

A study in Madagascar (Tingle & McWilliam, 1998; 1999) made an evaluation of the short-term impact on non-target organisms of two pesticides used during emergency locust control operations in Madagascar included the effects of fipronil (as Adonis 7.5 g ai./l) on birds.

Results from field counts showed that:

- There was no evidence of an impact of fipronil on the total number of birds observed during transect counts, nor on numbers of the two must abundant species, *Mirafa hova* (Madagascar bush lark) nor *Cisticola cherina* (Madagascar cisticola) throughout the period from spraying until the end of June.
- A general decline in the total numbers of birds in both control and sprayed plots between two weeks after spraying and eight weeks later was thought to be due to the seasonal drying out of the grasslands and falling temperatures.
- Although sample sizes were small, there was an indication of a deleterious effect on *Merops superciliosus* (Madagascar bee-eater) and *Falco newtoni* (Madagascar kestrel) in the fipronil sprayed plot. The relative abundance of *Merops superciliosus* declined during the first and second post-spray fortnights. There was no recovery 16 weeks later.
- There was a pronounced decline in the relative abundance of *Falco newtoni* in the plot sprayed with fipronil.
- There was a seasonal decline in the relative abundance of the Madagascar button quail (*Turnix nigricollis*) in all treatments during the post-spray period, although numbers of this bird were markedly higher in unsprayed plots.

In summary, "It should be noted that the indirect effects of pesticides (*i.e. on potential food source*) can take several months to appear when mediated through their food supply". " Insufficient data have been analysed to allow detection of such an effect".

No dead birds were recovered during the study and evidence is thus circumstantial, but clearly indicated a negative effect in the fipronil sprayed area when compared with another pesticide (IGR). Species reduction as a secondary effect (due to prey reduction) can not be ruled out (see below). There is a clear message that further

Further field-worked studies are ... needed on ... effects of fipronil on gallinaceous birds, insectivorous families of birds and on birds of prey.

investigations are needed, especially in view of the results obtained from the effects of fipronil on non-target invertebrate species such as termites and bees, which may be important food sources for birds (Tingle & McWilliam, 1999).

Large-scale insecticide tests were undertaken in Wyoming (USA) against grasshopper infestations (Lockwood *et al*., 1998), and a survey of impacts on birds showed that:

- ❖ No dead birds or failed nests were found after treatment, and relatively dense populations of birds persisted.
- ❖ Declines in bird densities relative to the control sites were observed, but in many cases, the absolute bird densities increased in the treated plots.
- ❖ Fipronil-Reduced Agent-Area Treatments (RAAT) (Lockwood & Schell, 1997) had least impact on birds of the 3 insecticides tested, perhaps due to the relatively higher arthropod densities maintained by higher swath spacing.
- ❖ At worst, bird populations tracked the decline in grasshopper populations; while at best, bird populations in treated plots exceeded those in the untreated controls.
- ❖ Fipronil apparently had less effect on total and insectivorous bird populations than did carbaryl or malathion.

Bird species involved in these studies are shown in Table 12.

However, these conclusions are based on only 3 surveys: one before spraying and two after (14 days and 28 days post-treatment, respectively). Such a superficial study can do little more than indicate any effects and cannot be regarded as conclusive, although it does show that catastrophic effects are unlikely.

Further field-worked studies are still needed to effectively evaluate the effects of this pesticide on non-target species of birds. There is particularly a need for data on gallinaceous birds to which fipronil is known to be highly toxic, on insectivorous birds from families which are not usually studied in standard toxicity test and on birds of prey (particularly falcons).

Table 13. Numbers of birds seen during a study of the effects of Reduced Agent-Area treatments with fipronil

	Numbers of birds seen in treated and untreated areas	
Species	**Pollet Ranch**	**Mooney Ranch**
Strunella neglecta	296	163
Pooecetes gramineus	19	48
Spizella passerina	3	9
Falco sparverius	0	16
Charadrius vociferus	4	2
Bartramia longicauda	4	6
Zonotrichia leucophrys	9	0
Amphispiza belli	3	5
Spizella breweri	21	0
Chondestes grammacus	1	99
Chordeiles minor	2	4
Quiscalus quiscula	0	4
Hirundo rustica	0	3
Tyrannus verticalis	0	8
Tyrannus tyrannus	0	10
Icterus galbula	0	2
Dendroica petechia	0	1
Tachycineta bicolor	0	3
Pipilo chlorurus	0	7
Colaptes auratus	0	3
Toxostoma rufun	0	5
Spizella arborea	0	2
Turdus migratorius	0	12
Melospiza melodia	0	7
Sialia currucoides	0	23
Hirundo pyrrhonota	0	1
Sayornis saya	0	1
Lanius ludovicianus	0	2
Ammodramus savannarum	0	3
Salpinctes obsoletus	0	3
Eremophila alpestris	347	0
Molothrus ater	1	9
Agelaius phoeniceus	0	7
Carduelis tristis	0	2
Passerian amoena	0	2
Calamospiza melanocorys	12	47
Zenaida macroura	11	30
Buteo jamaicensis	0	9

Mammals

There has been a significant amount of laboratory work undertaken on the toxicity of fipronil to mammals both in its technical and metabolite forms. The data indicate that there is some alteration of metabolic function in the thyroid, and in liver dimensions. However there is little conclusive data for carcinogenic activity except in rats where carcinogenic activity was found in thyroid glands at 300 ppm.

Technical material showed neurotoxic effects and was clearly more hazardous to the mammals in the studies undertaken. Commercial formulations seem to have little effect upon mammals.

Further field-worked studies are still needed to effectively evaluate the effects of this pesticide on non-target species, and further studies are required by the EPA.

Chronic toxicity

Technical fipronil caused a number of toxicological effects in chronic animal studies at relatively low doses.

"Clinical signs of neurotoxicity were reported in rats at doses as low as 0.07 mg/kg/day and dogs to 1.0 mg/kg/day. Clinical signs of neutotoxicity were also reported in a 21-day dermal exposure study in rabbits at 10mg/kg/day, indicating that neurotoxicity can result from dermal exposures. In a thyroxine clearance study in rats using technical fipronil at 10mg/kg/day by gavage, there was "no effect on mortality or other ante-mortem parameters" (New York State Department of Environment & Conservation,1996).

An acceptable chronic rat feeding study identified the following effects: seizures, including seizures resulting in death, decreased body

Technical fipronil caused a number of toxicological effects in chronic animal studies at relatively low doses.

Toxicology Characteristics: Technical Grade Fipronil (USEPA, 1996)

Acute oral (Rat): LD_{50} 97 mg/kg; Tox Category II
Acute dermal (Rabbit): LD_{50} 354 mg/kg; Tox Category II
Acute dermal (Rat): LD_{50} > 2000 mg/kg; Tox Category III
Acute inhalation (Rat): LC_{50} 0.39mg/L; Tox Category II
Primary eye irritation (Rabbit): Mild transient eye irritation clearing by 24 hours; Tox Category III
Primary dermal irritation (Rabbit): Slight dermal irritation; Tox Category IV
Dermal sensitization (Guinea Pig): Not a sensitiser

Toxicology Characteristics: End-use product (Chipco Choice Insecticide) (USEPA, 1996)

Acute oral (Rat): Estimated LD_{50}> 5000mg/kg; Tox Category IV
Acute dermal (Rabbit): Estimated LD_{50}> 2000mg/kg; Tox Category III
Acute inhalation (Rat): Estimated LC_{50}> 5.06mg/L; Tox Category IV
Primary eye irritation (Rabbit): Irritation clearing by 3rd day; Tox Category III
Primary Dermal Irritation (Rabbit): Slight irritation, clearing by 72 hours; Tox Category IV
Dermal Sensitization (Guinea Pig): Not a sensitiser

weight gain, decreased food consumption and food conversion efficiency, decreased hematology measures, alterations in clinical chemistry (cholesterol, calcium, and protein), alterations in thyroid hormones, alterations in urine chemistry, changes on gross necropsy, increase in liver and thyroid weights, and progressive senile nephropathy (kidney effects). The NOEL for systemic toxicity was 0.5 ppm. The LOEL of 1.5 ppm was based on an increase in incidence of clinical signs and alterations in clinical chemistry and thyroid parameters. Based on this study, the RfD Committee recommended that the RfD be established using the NOEL and an uncertainty factor of 100 to account for the interspecies extrapolation and intraspecies variability. The RfD was set at 0.0002 mg/kg/day (USEPA, 1996).

Subchronic Toxicity (Dog): NOEL = 2.0 mg/kg/day for males and 0.5 mg/kg/day for females. LOEL = 10.0 mg/kg/day for males (based on clinical signs of toxicity) and 2.0 mg/kg/day for females (based on clinical signs of toxicity and decreased body weight gain) (USEPA, 1996).

In rabbits, neurotoxicity can result from dermal exposures to fipronil.

Subchronic Toxicity (Rat): NOEL = 5 ppm for males (0.33 mg/kg/day) and females (0.37 mg/kg/day. LOEL 30 ppm for males (1.93 mg/kg/day) and females (2.28 mg/kg/day) based on alterations in serum protein values and increased weight of the liver and thyroid (USEPA, 1996).

Chronic Toxicity (Dog): NOEL 0.2 mg/kg/day. LOEL 2.0 mg/kg/day based on clinical signs of neurotoxicity and abnormal neurological examinations (USEPA, 1996).

Chronic Toxicity (Dog): NOEL = 0.3 mg/kg/day in females and 1.0 mg/kg/day in males. LOEL is 1.0 mg/kg/day in females and 2.0 mg/kg/day in males based on clinical signs of neurotoxicity (USEPA, 1996).

Acute Neurotoxicity (Rat): NOEL = 0.5 mg/kg for males and females. LOEL 5.0 mg/kg for males and females based on decreased hind leg splay at the 7 hour post treatment evaluation in males and females (USEPA, 1996).

Subchronic Neurotoxicity (Rat): NOEL = 5.0 ppm (0.301 mg/kg/day for males and 0.351 mg/kg/day for females). LOEL = 150 ppm (8.89 mg/kg/day for males and 10.8 mg/kg/day for females) based on increased incidence of no urination and increased incidence of exaggerated tail pinch response in males, increased incidence of exaggerated startle responses in males and females, and increased forelimb grip strength at week 13 in females (USEPA, 1996).

Metabolism (Rat): ^{14}C fipronil was administered orally in aqueous methylcellulose to male and female rats at doses of 4 and 150 mg/kg (single dose) and 4 mg/kg for 14 days (repeated dose). The rate and extent of absorption appeared similar among all dose groups, but may have been decreased at the high dose. Distribution data showed significant amounts of residual radioactivity in the carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post dose for all rats in all dose groups. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found but an increase in the amount in abdominal fat, carcass, and adrenals. Faeces appeared to be the major route of excretion where 45-75% of an administered dose was excreted. Excretion in urine was 5-25%. Increases in the percentages excreted in urine and faeces were observed with repeated low oral dosing or a single high dose, while the percentage found in all tissues combined decreased. There were no significant sex related differences in excretion. Major metabolites in urine included ring opened products of the metabolite MB 45897, two oxidation products, MB 46136 and RPA 200766, and the parent chemical fipronil. In faeces, the parent was detected as a significant fraction of the sample radioactivity as well as the oxidation products MB 46136 and MB 45950. Whole blood half-life ranged from 149.4 to 200.2 hours at 4 mg/kg. At 150 mg/kg, whole blood half-life was noticeably decreased to 54.4 hours in male rats and 51.2 hours in female rats (USEPA, 1996).

In addition to the toxicity endpoints identified above, the toxic endpoint selection (TES) committee has identified the following endpoints and dose levels of concern. The acute dietary endpoint of concern is acute neurotoxicity. The NOEL is 0.5 mg/kg, and the LOEL is 5.0 mg/kg based on decreased hind leg splay observed at this level at seven hours post treatment. The TES committee

... technical fipronil is not carcinogenic when administered at doses of 30 ppm or greater to mice.

also identified short and intermediate term occupational and residential exposure end points based on a 21-day dermal toxicity study. The NOEL was 5.0 mg/kg/day. The LOEL of 10.0 mg/kg/day was based on decreased body weight gain and food consumption in rabbits (USEPA, 1996).

It was also stated that the formulated products were not very toxic or irritating to laboratory animals in acute studies.

Dermal irritation NOEL >= 10.0 mg/kg/day. Systemic LOEL = 10 mg/kg/day based on decreased body weight gain and food consumption; Dermal irritation LOEL > 10 mg/kg/day (USEPA, 1996).

Carcinogenicity

Carcinogenicity (Mouse): NOEL = 0.5 ppm (0.055 mg/kg/day for males and 0.063 mg/kg/day for females). LOEL = 10 ppm (1.181 mg/kg/day for males and 1.230 mg/kg/day for females) based on decreased body weight gain, decreased food conversion efficiency (males), increased liver weights and increased incidence of hepatic histopathological changes. The study demonstrated that technical fipronil is not carcinogenic when administered at doses of 30 ppm or greater to CD-1 mice (USEPA, 1996).

Combined Chronic Toxicity/Carcinogenicity (Rat): NOEL = 0.5 ppm for males (0.019 mg/kg/day) and females (0.025 mg/kg/day). LOEL 1.5 ppm for males (0.059 mg/kg/day) and females (0.078 mg/kg/day) based on an increased incidence of clinical signs and alterations in clinical chemistry and thyroid parameters. The study demonstrated that fipronil is carcinogenic to rats at doses of 300 ppm in males (12.68 mg/kg/day) and females (16.75 mg/kg/day) (USEPA, 1996).

Genotoxicity (mutagenic effects)

Developmental toxicity studies in rats and rabbits showed that fipronil was not associated with significant developmental toxicity. Several mutagenicity tests were negative. They include two *Salmonella typhimurium*/mammalian microsome reverse gene mutation assays with and without S-9 activation, an in vitro cytogenics assay using human lymphocytes, two Chinese hamster forward gene mutation assays, and a mouse micronucleus test (USEPA, 1996);.an Ames (salmonella) test in the presence and absence of S9 activation; an in vitro gene mutation (Chinese hamster V79 cells)/HGPRT assay both with and without S9 activation; a cytogenic assay (Human lymphocytes) test of clastogenic effects with and without S9 activation; and a mouse micronucleus assay (USEPA, 1996).

... fipronil is carcinogenic to rats at doses of 300 ppm in males ... and females.

Reproductive effects

An acceptable reproductive toxicity study in rats showed that fipronil is associated with reproductive effects. The NOEL for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females). The LOEL for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on effects on the thyroid, liver, and pituitary gland. The NOEL for reproductive toxicity was 30 ppm (2.54 and 2.74 mg/kg/day for males and females respectively). The LOEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females based on clinical signs of toxicity, decreased litter size, decreased body weights, decrease in the percentage of animals mating, reduction in fertility index, reduced post-implantation survival and offspring postnatal survivability, and delay in physical development (USEPA, 1996).

Developmental Toxicity (Rat): Maternal toxicity NOEL = 4 mg/kg/day. Maternal toxicity LOEL = 20 mg/kg/day based on reduced body weight gain, increased water consumption, reduced food consumption and reduced food efficiency. Developmental toxicity NOEL is 20 mg/kg/day or higher. Developmental toxicity LOEL is greater than 20/mg/kg/day (USEPA, 1996).

Developmental Toxicity (Rabbit): Maternal toxicity NOEL < 0.1 mg/kg/day. Maternal toxicity LOEL is equal to or less than 0.1 mg/kg/day based on reduced body weight gain reduced food consumption and efficiency. Developmental toxicity NOEL is equal to or greater than 1.0 mg/kg/day. Developmental toxicity LOEL is greater than 1.0 mg/kg/day (USEPA, 1996).

Multigeneration Reproduction Study (Rat): NOEL for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females). LOEL for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on systemic signs including increase in the absolute and relative weights of the thyroid glands and liver in males and females of the F0 and F1 generations; decrease in the absolute weight of the pituitary gland in females in the F1 parental animals; and increase incidence of follicular epithelial hypertrophy of the thyroid glands in females of the F1 generation. The NOEL for reproductive toxicity was 30 ppm (2.54 and 2.74 mg/kg/day for males and females respectively). The LOEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females based on clinical signs of toxicity in the F1 and F2 offspring; decreased litter size in the F1 and F2 litters; decreased body weights in the F1 and F2 litters; decrease in the percentage of F1 parental animals mating; reduction in fertility index in F1 parental animals; reduced post-implantation survival and offspring postnatal survivability in the F2 litters; and delay in physical development in the F1 and F2 litters (USEPA, 1996).

In summary:

- fipronil is moderately toxic to laboratory animals by oral inhalation;
- fipronil is moderately toxic to laboratory animals by dermal routes of exposure;
- fipronil is mildly irritating to the eyes and skin of laboratory animals;
- technical fipronil is in toxicity Categories II and III and is classed as a non-sensitiser.
- technical fipronil showed clinical signs of toxicity & decreased weight gain;
- technical fipronil increase in thyroid & liver decreased weight. Caused a decreased weight of pituitary gland in female rats and an increase in follicular hypertrophy in males; there was also

Fipronil is moderately toxic to mammals by oral inhalation.

a decrease in litter size body weight
- no chronic toxicity to dogs was reported with the technical product
- at 300 ppm there were clinical signs & alterations in chemistry of thyroid (measured by an increase in thyroid follicular cell tumours) in rats with NOEL at 0.019 mg/kg/day, indicating carcinogenic action
- fipronil was not carcinogenic to female mice (CD-1) when administered at doses of 30 ppm.

A field study in Madagascar, studied the effects of fipronil (as Adonis 7.5 g ai./l) on small non-target mammals. There are a number of mammal species endemic to the island of Madagascar and the following insectivorous Tenrecidae were selected as indicator taxa:
- *Echinops telfairi*
- *Setifer setosus*
- *Geogale aurita*

Fipronil is moderately toxic to mammals by dermal exposure.

Data from field collections showed that there was no decline in numbers of *E . telfairi* and that there was no evidence of differential mortality from recaptures of marked animals. It was noted that more animals were recaptured in both of the treated plots which might have "indicated a greater reliance upon the bait in the traps, if (prey) insect abundance was reduced".

Geogale aurita is a specialist termite feeder and termites are hard-hit by fipronil, thus the risk to this species appears quite high. However there were not enough data to show any effects on this tenrec (Tingle & McWilliam, 1998).

Further work is essential in monitoring field use of fipronil to evaluate impacts on non-target mammals. Follow up studies in Madagascar have demonstrated adverse effects of cover sprayed fipronil on *E. telfairi* due to the food chain link (Peveling 2001). No data appear to be available on bats and yet, as insectivores, they may be at risk.

Endocrine disruption

As yet, there is no data or information on the potential of fipronil as an endocrine disrupter. This is under investigation (USEPA, 1998).

Data gaps

As yet, there is no data or information on the potential of fipronil as an endocrine disrupter (see above). The data base for the photodegradate MB 46513 is incomplete and hazard assessments are made by the USEPA based on the fipronil studies with an additional factor of 10 to adjust the NOEL figures. There also appears to be no research considering the role of MB 46513, when fipronil is used in a veterinary context.

… there are reports of old fipronil barrels being sold to private citizens in Madagascar. Uncleaned storage containers are a human health hazard.

The Advisory Committee on Pesticides (ACP) of the Pesticides Safety Directorate (PSD) identified the following data gaps for products containing fipronil (ACP, 2000):
- stability and integrity of the granule in the product,
- solubility, vapour pressure and octanol/water partition coefficient for certain breakdown products,
- risk to aquatic organisms,
- potential risk from residues in food if treated compost is disposed on to land where edible crops are grown.

Developing country issues

There are few issues unique to fipronil in relation to its use in developing countries - most are relevant to all pesticide use (see Rainbird & O'Neill, 1993). However, the following risks are noted in relation to fipronil because of its specific characteristics and the conditions and situations under which it may be used in less developed nations:

Climate - because of heat levels frequently encountered in the tropics the likelihood that spray operators will not use suitable protective clothing when applying fipronil or coming in contact with it shortly after application is increased. Due to the known irritant characteristics and possible human health hazards of certain formulations, this is an area of concern.

Container disposal - empty pesticide containers are useful and valuable assets in materially poor communities and are frequently taken for use as storage vessels,. They are rarely adequately cleaned beforehand. In Madagascar, for example, there are reports of old fipronil barrels being sold to private citizens (Anon, 2000g). Uncleaned storage containers are a human health hazard, so this must be considered an area of concern.

Illiteracy - problems associated with an inability to read label warnings on containers during use may lead to increased human health risks to spray operators. Over-dosing and the risks to organisms beneficial to agriculture and to non-target wildlife; over-dosing and/or insufficient harvest periods leading to excessive residues on crops; under-dosing leading to increased rate of build up of resistance in pests..

Unique, unusual and/or poorly known fauna - the wide differences in toxicity of fipronil to different (even closely related) animals means that risk assessment for areas with unusual fauna cannot be predicted without extensive studies on locally occurring species. The need for incorporation of data on indigenous species in risk assessment in semi-arid regions, especially temporary ponds has been emphasised (Everts, 1997; Lahr, 1997).

Poor ecological knowledge - where little is known of the ecology of habitats likely to be treated with fipronil, adequate predictions cannot be made for effects on wildlife nor the implications for the structure and functioning of the ecosystem.

Risks

The potential risk to birds, fish and aquatic invertebrates associated with the use of fipronil as a pre-planting soil treatment for rice were investigated and calculated using an interim, first-approximation dilution model. The model predicted the maximum concentration of fipronil in paddy water is unlikely to exceed 5.32 mg/l. Risk assessment undertaken indicated that fipronil concentrations in wildlife food items are not likely to represent high acute risk for non-endangered bird species. However, should endangered bird species be

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exposed, then exposure levels would be above the Environmental Fate and Effects Division (EFED) level of concern for acute effects. With the exception of predicted values on short grass, no chronic exposure risks showed above the EFED level of concern for birds (USEPA, 1999).

In-paddy water concentrations of fipronil and its degradates trigger the endangered species acute level of concern for freshwater fish and invertebrates for both fipronil and the degradate MB46513 (USEPA, 1999).

Predicted rice paddy water concentrations of fipronil, MB46135, MB46136 and MB45950 exceed the acute toxicity thresholds for estuarine invertebrates. The predicted levels are not high enough to trigger chronic exposure effects for freshwater species, but they do for both estuarine fish and invertebrates. This assessment does not factor in dilution effects in receiving water. However, dilution factors would have to exceed 1000 for risk to estuarine invertebrates to fall below EFED levels of concern (USEPA, 1999).

Risk assessments indicate that fipronil concentrations in wildlife food items are not likely to represent high acute risk for non-endangered bird species. However, should endangered bird species be exposed, ... levels of concern for acute effects would be exceeded.

Conclusion

Fipronil is a highly effective, broad-spectrum insecticide with potential value for the control of a wide range of crop, public hygiene, amenity and veterinary pests. It can generally be applied at low to very low dose rates to achieve effective pest control.

The development of resistance and cross-resistance are potential problems resulting from the over-use of any pesticides and fipronil is relatively new and thus currently free from this problem. There are however indications that the root for resistance mechanisms (particularly to dieldrin resistant strains) is already apparent. Fipronil's use in conjunction with piperonyl butoxide (PB) should be avoided, as this is likely to speed the onset of resistance to fipronil due to the antagonism between the two chemicals.

Fipronil degrades slowly on vegetation and relatively slowly in soil and in water, with a half-life ranging between 36h and 7.3 months depending on substrate and conditions. It is relatively immobile in soil and has low potential to leach into groundwater.

One of its main degradation products, fipronil desulfinyl, is generally more toxic to a variety of animals than the parent compound and is very persistent.

There is evidence that fipronil and some of its degradates may bioaccumulate, particularly in fish. Further investigation on bioaccumulation is warranted, especially for the desulfinyl degradate.

Testing on local species seems particularly important in determining suitability of fipronil-based products for registration in different countries or habitats and the potential associated risk to non-target wildlife.

Maximum residue levels (MRLs) in food products range from 0.01 to 1.5 ppm depending on the animal or crop product; whilst the Acceptable Daily Intake (ADI) for humans range between 0.00003 mg/kg bw/day (prospective) for fipronil desulfinyl to 0.0002-0.00025 mg/kg bw/day for fipronil.

Questions have been raised about the suitability of fipronil for use in IPM, and the results from a range of studies carried out to date suggest that this must be evaluated on a case by case basis. In certain situations fipronil may disrupt natural enemy populations, depending on the groups and species involved and the timing of application.

Its acute toxicity varies widely, even in animals within the same groups. This means that the toxicological findings from results on standard test animals are not necessarily applicable to animals in the wild, especially in the more arid ecosystems (van der Valk, 1997). This is particularly true for birds, fish, amphibians and reptiles. Commonly tested soil dwelling invertebrates such as earthworms have little relevance in arid ecosystems, where termites, ants and a variety of beetles fulfil the functions of earthworms. (van der Valk, 1997). Testing on local species seems particularly important in determining suitability of fipronil-based products for registration in different countries or habitats and the potential associated risk to non-target wildlife.

The use of fipronil requires careful consideration where contamination of the aquatic environment is likely, due to its high toxicity to some fish and aquatic invertebrates. It is classified as "dangerous to fish and other aquatic life" on certain product labels.

Fipronil is very highly toxic to termites and has severe and long lasting negative impacts on termite populations. It thus presents a long-term risk to nutrient cycling and soil fertility where termites are "beneficial" key species in these ecological processes. Its toxicity to termites also increases the risk to the ecology of habitats in which termites are a dominant group, due to their importance as a food source to many higher animals.

Fipronil is highly toxic to bees and should not be used where it may affect foraging bees.

Risk assessment predictions have shown that some fipronil formulations present a risk to endangered bird, fish and aquatic and marine invertebrates. Great care should thus be taken in using these formulations where they may impact any of these endangered wildlife groups.

The dose levels at which fipronil produces thyroid cancer in rats are very high and unlikely to occur under normal conditions of use. There is also dispute as to whether this is relevant to human health risk. However, as fipronil is a relatively new insecticide that has not been in use for long enough to evaluate the risk it may pose to human health, from data on human exposure to the product, a precautionary approach may be warranted. This is particularly relevant in the situation in developing countries where illiteracy, lack of protective clothing and use of insecticide drums for water and food storage, increase the risk of human contact with the product at above recommended dose rates.

The use of some fipronil-based products on domestic animals is not recommended where handlers spend significant amounts of time grooming or handling treated animals.

In general, it would appear unwise to use fipronil-based insecticides without environmental monitoring to accompany their use, in situations, regions or countries where it has not been used before and where its use may lead to its introduction into the wider environment or bring it into close or direct contact with people.

Further work is needed on the impacts of fipronil on non-target vertebrate fauna (amphibia, reptiles, birds and mammals) before the risk to wildlife from this insecticide can be adequately assessed.

Further field study of the effects of fipronil on beneficial termites is required in order to assess the ecological impacts of the known toxicity of fipronil to these insects. Studies in Madagascar have now demonstrated adverse effects on certain lizards and mammals and confirmed a link to the severe adverse impact on termite populations, resulting in recommendations against its use for locust control in Madagascar (Peveling 2001).

Risk assessment predictions have shown that some fipronil formulations present a risk to endangered bird, fish and aquatic and marine invertebrates. Great care should thus be taken in using these formulations where they may impact any of these endangered wildlife groups.

As fipronil is a relatively new insecticide that has not been in use for long enough to evaluate the risk it may pose to human health, from data on human exposure to the product, a precautionary approach may be warranted.

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Fipronil profile

Pesticide Type:	Insecticide
Chemical Family:	Phenyl pyrazole
Producer:	Aventis Crop Science SA (ex-Rhone Poulenc SA)
Generic Name:	5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile
Common Name:	fipronil
Trade Name:	Fipronil Technical; and many others (see page 1, column 1)

(USEPA, 1996)

Chemical formulation

Chemical Characteristics: Technical Grade fipronil (USEPA, 1996)

Physical:	Powder
Colour:	White
Odour:	Mouldy

Melting Point:	195.5 to 203 °C
Density:	1.6262 g/ml at 20 °C
Molecular Formula:	$C_{12}H_4Cl_2F_6N_4OS$
Vapour Pressure:	2.8 x 10^{-9}mm Hg at 25 °C
Octanol/Water Partition Coefficient:	log PO/W = 4.01 pH: 5.9 to 6.1 at 23°C (1% w/v water)

Solubility:	**Solvent**	**Solubility (g/l)**
	water pH 5	0.0024
	water pH 9	0.0022
	acetone	545.9
	2-propanol	36.2
	dichloromethane	22.3
	ethyl acetate	264.9
	hexane	0.028
	methanol	137.5
	toluene	3.0
	octanol	12.2

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