NPIC Technical Fact Sheets are designed to provide information that is technical in nature for individuals with a scientific background or familiarity with the regulation of pesticides by the U.S. Environmental Protection Agency (U.S. EPA). This document is intended to be helpful to professionals and to the general public for making decisions about pesticide use. Call NPIC at 1-800-858-7378.

National Pesticide Information Center

Fipronil

(Technical Fact Sheet)

The Pesticide Label: Labels provide directions for the proper use of a pesticide product. *Be sure to read the entire label before using any product.* A signal word on each product label indicates the product's short-term toxicity.

CAUTION- low toxicity **WARNING- moderate toxicity** **DANGER- high toxicity**

What is fipronil?

- Fipronil is a broad-spectrum phenylpyrazole insecticide, toxic by both contact and ingestion in insects (1,2).
- Fipronil is the common name for the chemical 5-amino-1-(2,6-dichloro-α,α,α-trifluoro-*p*-tolyl)-4-trifluoromethylsulfinylpyrazole-3-carbonitrile. The Chemical Abstracts Service (CAS) number is 120068-37-3.
- Technical grade fipronil is a white powder with a moldy odor, has low solubility in water, and is stable to heat, air, and acidic conditions. Fipronil is subject to photodegradation and breaks down slowly under basic conditions (1,2).
- Fipronil was first registered for use by the U.S. Environmental Protection Agency (EPA) in May 1996. Currently, 49 registered products contain fipronil as an active ingredient (2,3).

How is fipronil used?

- Fipronil is used to control ants, cockroaches, termites, weevils, beetles, fleas, ticks, and other insects (1,3).
- Fipronil is used in granular turf products, seed treatments, topical pet care products, gel baits, liquid termiticides, and in agriculture (3).

What are some products that contain fipronil?

- Product names include Termidor, Frontline, Combat, Regent, Maxforce, and Chipco (3).
- Signal words for products containing fipronil range from Caution to Warning. The signal word reflects the combined toxicity of the active ingredient and other ingredients in the product (3). See the **Pesticide Label** box above and refer to the NPIC fact sheets on ***Signal Words*** and ***Inert or "Other" Ingredients***.

What is the mechanism of action of fipronil?

- Fipronil blocks $GABA_A$-gated chloride channels that are responsible for inhibition of the nervous system. Disruption of the $GABA_A$ receptors by fipronil allows excess neural stimulation to occur, resulting in the death of the target insect. Fipronil is designed to be effective by contact or ingestion (1,4-6).
- The $GABA_A$ receptors are pentameric transmembrane protein complexes. Other subunits in the $GABA_A$ complex

modify binding affinities and vary according to species (4,7,8).

- Due to differences in the composition of $GABA_A$ receptor subunits, fipronil has a higher affinity for insect receptor complexes compared to mammalian complexes. The lower affinity for mammalian receptors enhances selectivity and increases the margin of safety for people and animals (4,7-9).

- Fipronil-sulfone, the primary metabolite observed in armyworms, mice, and human liver microsomes (*in vitro*), has been reported to be 20 times more active at mammalian chloride channels than the parent compound (10-12).

  Fipronil readily photodegrades in the environment to fipronil-desulfinyl, which is reportedly 10 times more active at the mammalian chloride channel than the parent compound. The increased activity of the desulfinyl derivative at the GABA receptor reduces the selectivity between insects and humans (9,10).

What is the acute toxicity of fipronil?

Toxicity Category (*Signal Word*)

	High Toxicity (*Danger*)	Moderate Toxicity (*Warning*)	Low Toxicity (*Caution*)	Very Low Toxicity (*Caution*)
Oral LD_{50}	Less than 50 mg/kg	50 - 500 mg/kg	500 - 5000 mg/kg	Greater than 5000 mg/kg
Inhalation LC_{50} - 4hr	Less than 0.05 mg/L	0.05 - 0.5 mg/L	0.5 - 2.0 mg/L	Greater than 2.0 mg/L
Dermal LD_{50}	Less than 200 mg/kg	200 - 2000 mg/kg	2000 - 5000 mg/kg	Greater than 5000 mg/kg
Eye Effects	Corrosive	Irritation persisting for 7 days	Irritation reversible within 7 days	No irritation
Skin Effects	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours

Oral

- Technical grade fipronil is considered moderately toxic by ingestion based on animal studies with an oral LD_{50} of 97 mg/kg in rats and an LD_{50} of 95 mg/kg in mice (1). See boxes on **Laboratory Testing, Toxicity Category, and LD_{50}/LC_{50}**.

- The No Observable Adverse Effects Level (NOAEL) for acute neurotoxicity in rats fed a single dose of fipronil was 2.5 mg/kg (31).

- Signs of acute neurotoxicity (LOAEL) were seen in rats after 7 hours at a dose of 7.0 mg/kg/day (31).

Dermal

- Fipronil is considered low to moderate in toxicity by contact based on animal studies. The dermal LD_{50} was greater than 2000 mg/kg in rats and 354 mg/kg in rabbits. No systemic effects were observed (NOAEL) in a 21-day dermal toxicity study with rabbits at 5.0 mg/kg/day (31).

- Fipronil may cause slight skin or eye irritation that typically clears within 24 hours. Fipronil was not found to be a skin sensitizer when tested on Guinea Pigs (2).

Inhalation

- Fipronil is considered low to moderate in toxicity by inhalation with the 4 hr LC_{50} ranging from 0.39 to 0.682 mg/L in studies with rats (1,2).

Intraperitoneal (ip)

- In one study, fipronil was reported to have a 24 hr ip LD_{50} of 41 mg/kg in mice (9).

Signs of Toxicity - Animals

- Fipronil targets the nervous system. Signs of toxicity during an acute mouse feeding study with 87.4-97.2% fipronil included overactivity, irritability, convulsions, and death. Signs of toxicity during a chronic rat feeding study included reduced feeding, reduced body weight gain, seizures (including seizures resulting in death), alterations in thyroid hormones, and alterations in the mass and function of the liver, thyroid, and kidneys (2,13, 31).

LD50/LC50: A common measure of acute toxicity is the lethal dose (LD50) or lethal concentration (LC50) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD50 is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC50 is often expressed as mg of chemical per volume (e.g., liter (l)) of medium (i.e., air or water) the organism is exposed to. Chemicals are considered highly toxic when the LD50/LC50 is small and practically non-toxic when the value is large. However, the LD50/LC50 does not reflect any effects from long-term exposure (i.e., cancer, birth defects, or reproductive toxicity) that may occur at levels below those that cause death.

- Mice injected intraperitonealy with fipronil exhibited tonic-clonic seizures, facial clonus, or head twitching (4,14).

- Other reported adverse effects of fipronil reported in animal studies for oral or inhalation exposure include ataxia, over- or underactivity, twitching, tremors, excessive salivation, and hunched appearance (6).

Laboratory Testing: Before pesticides are registered by the U.S. EPA, they must undergo laboratory testing for short-term and long-term health effects. In these tests, laboratory animals are purposely fed a pesticide at high doses to cause toxic effects. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in cases of overexposure. When pesticide products are used according to label directions, toxic effects are not likely to occur because the amount of pesticide that people and animals may be exposed to is low compared to the doses fed to laboratory animals.

Signs of Toxicity - Humans

- Clinical signs and symptoms reported after ingestion of fipronil by humans include sweating, nausea, vomiting, headache, abdominal pain, dizziness, agitation, weakness, and tonic clonic-seizures. Clinical signs of exposure to fipronil are generally reversible and resolve spontaneously (15-17). See **Exposure** box.

- In one case report, a 50-year old man complained of headache, nausea, vertigo, and weakness after spraying his field with a fipronil product for 5 hours. Symptoms were reported to have developed after 2 hours and resolved spontaneously. The authors suggested inhalation or dermal contact as the route(s) of exposure, although there were no signs of conjunctivitis or skin irritation (18).

Are the metabolites of fipronil toxic?

- The primary metabolite of fipronil in armyworms, mice, and humans is fipronil-sulfone, which binds to the GABA receptor with an affinity 6 times greater than the parent compound. Fipronil and its sulfone have similar toxicity in mammals; the mouse ip LD_{50} 24 h after treatment is 41 and 50 mg/kg for fipronil and its sulfone, respectively (1,9,10,12).

- Fipronil-desulfinyl, the primary photoproduct in the environment, is 9-10 fold more potent and more acutely toxic than fipronil with an ip LD_{50} of 23 mg/kg in mice (9,10).

- Fipronil-desulfinyl is classified as Toxicity Category I for acute oral toxicity in rats, with an LD_{50} of 15 and 18 mg/kg for females and males, respectively (19).

Cancer: The U.S. EPA has strict guidelines that require testing of pesticides for their potential to cause cancer. These studies involve feeding laboratory animals large *daily* doses of the pesticide over most of the lifetime of the animal. Based on these tests, and any other available information, EPA gives the pesticide a rating for its potential to cause cancer in humans. For example, if a pesticide does not cause cancer in animal tests, then the EPA considers it unlikely the pesticide will cause cancer in humans. Testing for cancer has not been done on human subjects.

Is fipronil a carcinogen?

Animals

- Mice given fipronil in their diet for 2 years showed no evidence of carcinogenicity at doses of 30 ppm (20).

- Researchers administered fipronil in the diet of rats for 2 years. Carcinogenicity was observed at 12.68 mg/kg/day in males and 16.75 mg/kg/day in females based on an increased incidence of clinical signs and alterations in clinical chemistry and thyroid parameters (2).

- In one study, rats were fed 0, 0.5, 2, 6, and 10 ppm (0, 0.025, 0.098, and 0.050 mg/kg/day males, and 0, 0.032, 0.13, and 0.55 mg/kg/day females) fipronil-desulfinyl (the primary photodegradate), for 2 years. Male rats at 10 ppm and female rats at 2, 6, and 10 ppm developed clinical signs of toxicity with no evidence of carcinogenicity (13).

Humans

- The EPA classified fipronil as a Group C (possible human) carcinogen, based on increased thyroid follicular cell tumors in both sexes of rats (31).

- Fipronil did not cause mutations in human lymphocytes, Chinese hamster V79 cells, salmonella (Ames test), or mouse micronuclei (2).

Can fipronil cause reproductive or teratogenic effects?

Animals

- In one study with rats, no observable effects were recorded at 30 ppm (2.54 mg/kg/day in males, and 2.74 mg/kg/day in females; route of exposure not included). The lowest dosage at which reproductive effects were recorded was 300 ppm (26.0 mg/kg/day in males and 28.4 mg/kg/day in females; route of exposure not included) based on clinical signs of toxicity, decreased litter size, decreased body weights, decrease in percentage of animals mating, reduction in fertility index, reduced post-implantation survival and offspring postnatal survivability, and delay in physical development (2).

- In a dietary short-term developmental neurotoxicity study, the Lowest Observable Adverse Effect Level was 0.90 mg/kg/day based on a decrease in mean pup weights during lactation and a significant increase in the time of preputial separation in males (31).

- Other experimental studies with ingestion of fipronil have not reported significant alterations on animal development. There were no observable adverse effects within the limits of two studies performed using rats and rabbits. The Lowest Observable Adverse Effect Levels (LOAELs) were the highest doses tested: ≥20 and ≥1.0 mg/kg/day in rats and rabbits, respectively (2,6).

Could chronic exposure to fipronil cause health effects?

Animals

- No signs of systemic toxicity (NOEL) were observed in rats ingesting 0.5 ppm (0.019-0.025 mg/kg/day) during a 52-week chronic dietary study. The lowest dosage at which effects were observed (LOEL) was 1.5 ppm (0.059 mg/kg/day males, 0.078 mg/kg/day females), and included increased incidence of seizures and death, alteration in clinical chemistry (protein), and alterations in thyroid hormones (20, 31).

Exposure: Effects of fipronil on human health and the environment depend on how much fipronil is present and the length and frequency of exposure. Effects also depend on the health of a person and/or certain environmental factors.

- Dogs fed 0.2 mg/kg/day fipronil showed no adverse effects during one chronic feeding study (length unknown). In the same study, researchers observed clinical signs of neurotoxicity at 2.0 mg/kg/day (2).

- In one study, rats were fed 0, 0.5, 2, and 10 ppm (0, 0.025, 0.098, and 0.050 mg/kg/day males, and 0, 0.032, 0.13, and 0.55 mg/kg/day females) fipronil-desulfinyl (the primary photodegradate) for 2 years. Male rats at 10 ppm and female rats at 2, 6, and 10 ppm developed clinical signs of toxicity including aggression, irritability, excessive salivation, and convulsions. No effects were seen at or below 0.5 ppm (0.025 mg/kg/day) (13).

Humans

- The No Observed Effect Level (NOEL) for chronic systemic toxicity (0.5 ppm or 0.019 mg/kg/day) was divided by an uncertainty factor of 100 to estimate a reference dose (RfD) of 0.0002 mg/kg/day fipronil and/or fipronil-desulfinyl. This is the amount of fipronil that humans could be exposed to every day with no appreciable risk of adverse effects (31).

- Human chronic exposure data are not available.

Does fipronil disrupt the endocrine system?

- No data are currently available.

What is the fate of fipronil in the body?

Absorption

- In one study of dermal absorption, researchers applied a 79% solution of ^{14}C-fipronil to the backs of shaved rats. Test samples showed radiolabeled fipronil in blood, carcass, cage wash and wipe, urine, and feces. Researchers found less than 1% of the applied dose was absorbed after 24 hours at all doses tested (6).

- In an *in vitro* study of ^{14}C-fipronil absorption through human, rabbit, and rat epithelial membranes, researchers recorded penetration rates after 8 hours of 0.08% (rat), 0.07% (rabbit), and 0.01% (human) of the dose of 200 g/L fipronil solution. Researchers reported greater absorption from a 0.2 g/L solution of fipronil, with 0.9% (rat), 13.9% (rabbit), 0.9% (humans) of the dose being absorbed (6).

- In another *in vitro* study, researchers measured 0.15-3% penetration of a fipronil dose through human epidermal membranes after 24 hours. The percentage of the dose of fipronil penetrating rat epidermal membranes was measured as 1-35% after 24 hours. Variation in absorption depended upon formulation (21).

- A spot-on treatment study with ^{14}C-fipronil on dogs and cats reported that radio-labeled fipronil was distributed primarily in the superficial skin layers. Radio-labeled fipronil was recorded neither in the dermis nor the hypodermis (adipose tissue) (22).

- Approximately 0.2 - 7.0% of a fipronil-desulfinyl dose penetrated the skin of rats over a period of 24 h (13).

- Researchers placed radiolabeled fipronil in goat feed at 0.05, 2, and 10 ppm for 7 days. Absorption of fipronil from the feed ranged from 15-33%. A study in rats found absorption rates after oral administration between 30-50% (6).

Distribution

- Fipronil is widely distributed in mammals and is found predominantly in fatty tissues. Rats given a single oral dose had the highest concentrations of fipronil in the stomach, GI tract, fat, and adrenals. Moderate levels were found in the liver, pancreas, thyroid, and ovaries. Low levels were present in the muscle, brain, heart, and cardiac blood (2,6).

- A spot-on treatment study with ^{14}C-fipronil on dogs and cats reported radioactivity 2 months after treatment concentrated in the sebaceous glands, epithelial layers surrounding the hairs, and exposed part of the hair shaft, suggesting the passive diffusion of fipronil in the sebum covering hair and skin (22).

- Researchers applied a spot-on fipronil product to dogs and vigorously petted them for 5 minutes every day with cotton gloves to mimic normal exposures to treated animals. Residues transferred to the gloves peaked at 589 ± 206 ppm fipronil 24 h after treatment, decreased steadily over time (448 ± 118 ppm after 8 days) , and were undetectable after 36 days (17).

Metabolism

- The whole-blood half-life of fipronil in rats ranged from about 6.2-8.3 days after a single 4 mg/kg oral dose and decreased significantly to 2.1-2.3 days after a single 150 mg/kg oral dose (2). See **Half-life** box.

- The primary metabolite of fipronil in animals is the fipronil-sulfone derivative. Researchers injected mice with fipronil and detected the sulfone derivative in the brain, liver, kidney, fat, and feces (6,10).

- Fipronil-desulfinyl, the primary photodegradate of fipronil, has been measured in the fat, brain, liver, kidney, skin, and feces of mice, rats and lactating goats after oral exposure or injection (6,10,13).

Excretion

Rats given an oral dose of fipronil excreted 45-75% in the feces and 5-25% in the urine. The parent compound and the oxidation product, fipronil-sulfone, were present in both (2,6).

- Lactating goats ingesting fipronil for 7 days excreted 18-64% of the compound in the feces and 1-5% in milk; 8-25% remained in body tissues (6).

- Goats dosed with fipronil-desulfinyl excreted 20-50% in feces and 3-7% in the urine (13).

Half-life is the time required for half of the compound to degrade or be eliminated from the body.

1 half-life	**=**	**50% remaining**
2 half-lives	**=**	**25% remaining**
3 half-lives	**=**	**12% remaining**
4 half-lives	**=**	**6% remaining**
5 half-lives	**=**	**3% remaining**

Remember that the amount of chemical remaining after a half-life will always depend on the amount of the chemical originally applied.

Does fipronil degrade indoors?

- No data were found.

What is the environmental fate of fipronil?

Soil

- The half-life of fipronil has been measured at 122-128 days in aerobic soils. Under aerobic conditions, naturally occurring soil organisms break down fipronil to form fipronil-sulfone. Fipronil can also be hydrolyzed to form fipronil-amide (2). See **Half-life** box.

- Fipronil degrades on soil surfaces from ultraviolet radiation (i.e. sunlight) to form fipronil-desulfinyl, and has a measured half-life of 34 days in loamy soil. However, soil particles may prevent light from penetrating any significant depth under field conditions and increase residence time. There was no evidence of volatility of fipronil and its metabolites (2,23).

- Fipronil has low mobility in soil and is not expected to leach into groundwater. After soil treatment, fipronil usually does not travel further than the upper 6 inches of soil, and significant lateral movement is not expected (1,2,24).

- K_{OC} values for fipronil range from 427-1248 in sandy loam but will vary depending on clay and organic carbon content. The K_{OC} is 3946 ± 2165 for fipronil-sulfide and 2010 ± 1370 for fipronil-desulfinyl (1,24).

Water

- Fipronil degrades rapidly in water when exposed to UV light to form fipronil-desulfinyl. Under these conditions, fipronil has a half-life of 4 to 12 hours (23,25).

- Fipronil is stable to hydrolysis at pH 5 and pH 7. However, it degrades in alkaline conditions in direct proportion to increasing pH values. Fipronil-amide is the primary residue formed from hydrolysis (2,23,25).

- Fipronil was measured in surface water at concentrations of 0.829 to 5.29 µg/L in southwestern Louisiana during March through April, which corresponds to the release of ricefield tailwater. Results indicate that fipronil degradation products accumulate in river bed sediment while the parent compound does not (32).

- Fipronil-desulfinyl photodegrades in aerated and static water with recorded half-lives of 120 ± 18 and 149 ± 39 hours, respectively (25).

- Fipronil and fipronil-desulfinyl are less volatile than water and can concentrate under field conditions (1,2).

Air

- The vapor pressure for fipronil is 3.7×10^{-4} mPa (25ºC). Photodegradation studies in soil found no evidence of volatility of fipronil or its metabolites (1,2).

Plants

- Fipronil is not well absorbed by plants after soil treatment (about 5%) and partially degrades in plants to the sulfone and amide derivatives. Fipronil applied to foliage partially photodegrades to form fipronil-desulfinyl (1).

Does fipronil affect wildlife?

Birds

- Fipronil is highly toxic to bobwhite quail and pheasants, with an acute oral LD_{50} of 11.3 mg/kg and 31 mg/kg, respectively. Fipronil also has high sub-acute toxicity with a 5-day dietary LC_{50} of 49 mg/kg in quail (1,2).

- Fipronil is practically non-toxic to mallard ducks and has no documented acute, sub-acute, or chronic effects (1,2).

- The fipronil-sulfone metabolite is highly toxic to upland game birds and moderately toxic to waterfowl by ingestion (2).

Fish and Aquatic Life

- Fipronil is highly to very highly toxic to marine and freshwater fish. The 96-hour LC_{50} is .246 mg/L for rainbow trout, 0.083 mg/L for bluegill sunfish, and 0.13 mg/L for sheepshead minnows (1,2).

- Fipronil-sulfone is 6.3 and 3.3 times more toxic than the parent compound to rainbow trout and bluegill sunfish, respectively (2).

- Fipronil accumulates in fish with a bioconcentration factor of 321 for whole fish, 164 for edible tissue, and 575 for non-edible tissue. Fish eliminated fipronil completely 14 days after being transferred to clean water. The primary metabolites in fish are fipronil-sulfone and –sulfide (2).

- Fipronil is highly toxic to freshwater invertebrates. In daphnids, no observable effects (NOEL) were measured at 9.8 µg/L and the Lowest Observed Effect Level (LOEL) for fipronil was 20 µg/L. The sulfone and desulfinyl metabolites are 6.6 and 1.9 times more toxic to freshwater invertebrates, respectively, compared with fipronil (2).

- In one study, male copepods reared in a 0.63 µg/L fipronil solution had a 75-89% decrease in reproductive success. Carry-over effects were significant for males (but not females) moved to clean seawater three days before mating (26).

- Fipronil is highly toxic to oysters with an EC_{50} of 0.77 mg/L and very highly toxic to mysid shrimp with a 96-hours LC_{50} of 140 ng/L. Exposure to less than 5.0 ng/L fipronil affected mysid growth, reproduction, and survival (2).

- When applied to water, fipronil varies greatly in its toxicity and potential to bioaccumulate in aquatic arthropods depending, on the species (27).

Terrestrial Invertebrates

- Fipronil is highly toxic to honeybees by contact and ingestion when applied to plant foliage (1).

- Researchers found fipronil killed 38.8 - 94.5% of beneficial predators such as *Orius spp.* (flower bug) and *Geocoris spp.* (big-eyed bug) and significantly reduced reproductive success and prey consumption when applied at labeled rates (28).

- When applied to fields for locust control, fipronil killed >90% of the resident nontarget insects *Carabidae, Tenebrionidae, Scelionidae,* and *Sphecidae* populations in 2 days. Recolonization was very poor for 2-4 weeks, depending on the application rate (29).

- Fipronil treated soil is non-toxic to worms, including earthworms of the *Pheretima* group (1,30).

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