● INSECTICIDE FACTSHEET

FIPRONIL

Fipronil is a relatively new insecticide. It is used in cockroach baits and gels, flea products for pets, ant baits and gels, termite control products, turf and golf course products, and agricultural products.

Symptoms of exposure to fipronil include headache, nausea, dizziness, weakness, and sometimes eye irritation and eye injury. In pets, poisoning symptoms include irritation, lethargy, incoordination, and convulsions.

In tests with laboratory animals, fipronil caused aggressive behavior, damaged kidneys, and "drastic alterations in thyroid function." The fipronil-containing product Frontline caused changes in the levels of sex hormones.

The offspring of laboratory animals exposed to fipronil during pregnancy were smaller than those of unexposed mothers. They also took longer to mature sexually.

The U.S. Environmental Protection Agency classifies fipronil as a carcinogen because exposure to fipronil caused benign and malignant thyroid tumors in laboratory animals.

One of fipronil's breakdown products is ten times more toxic than fipronil itself.

People can be exposed to fipronil when they pet an animal that has received a flea treatment. Fipronil persists for at least 56 days on pets.

Studies of fipronil contamination of water are limited, but it has been found in rivers near rice fields where it is used in Louisiana. It has also been found in an urban stream in Washington.

Fipronil is toxic to birds, lizards, fish, crawfish, shrimp, bees, and other animals. Minute concentrations (as low as five parts per trillion) have caused adverse effects.

BY CAROLINE COX

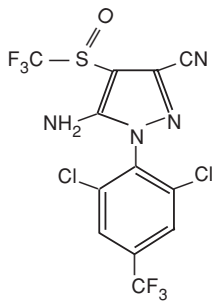
Fipronil (see Figure 1) is an insecticide in the phenyl pyrazole chemical family, a pesticide family with only a few chemicals.[1] It was first marketed in the U.S. in 1996[2] and is sold under a variety of brand names including Frontline, Regent, Termidor, Combat, and Maxforce.[3] Companies that sell fipronil-containing insecticide products include Bayer Environmental Science, BASF Corporation, and Merial Limited.[3]

Uses

Fipronil is used in fire ant baits, cockroach baits and gels, flea products for dogs and cats, ant baits and gels, termite control products, turf and golf course products, and agricultural products.[2,3]

There is no publicly available information about how much fipronil is currently used in the U.S.

Figure 1
Fipronil



5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1-R,S)(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile

How Does Fipronil Kill Insects?

Fipronil has a different mode of action than many common insecticides.[4] It is "an extremely active molecule." In insects, it disrupts the nerves in the brain and spinal cord by interfering with the ability of these nerve cells to transmit nerve impulses. The result is uncontrolled activity leading to death of the insect.[1]

Fipronil also disrupts nerves in animals other than insects, including humans, but it does not bind as tightly to these nerve cells as it does to insect nerve cells.[1]

"Inert" Ingredients

Like most pesticides, commercial fipronil products contain ingredients other than fipronil. According to U.S. pesticide law, these ingredients are

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called "inert."[5] Publicly available information about the identity of these ingredients is sparse.

For information about the hazards of some of the identified inert ingredients in commercial fipronil products, see "Inert Ingredients," below.

Research studies about fipronil sometimes use commercial fipronil products, but mostly use fipronil alone. In this article we identify which was used in each study we discuss.

Symptoms of Poisoning in Humans and Pets

Physicians at the Medical University of Gdansk (Poland), report that symptoms of poisoning due to exposure to fipronil-containing insecticides include headache, nausea, dizziness, and weakness.[6] In addition, four fipronil products cause eye irritation and two cause eye injury.[7-12]

According to the U.S. Environmental Protection Agency (EPA), pets treated with fipronil flea products have developed skin irritation, lethargy, incoordination, dilated pupils, facial swelling, and convulsions. While these symptoms are rare, certain animals (Bichon Frise dogs, for example) seem to be particularly sensitive to fipronil.[13]

Neurotoxicity in Laboratory Animals

Fipronil exposure caused a variety of nervous system problems in laboratory tests. A fipronil manufacturer sponsored a study in which rats were fed fipronil for their expected lifetime (two years). The study found signs of neurotoxicity, including aggressive behavior, at all dose levels tested.[14] (See Figure 2.)

Effects on Kidneys

Fipronil exposure also caused kidney damage in tests of laboratory animals. The study mentioned above showed that fipronil exposure increased both the incidence and severity of damaged kidneys. The incidence of kidney damage increased at the two highest dose levels tested; the severity of damage increased at all dose levels tested.[15]

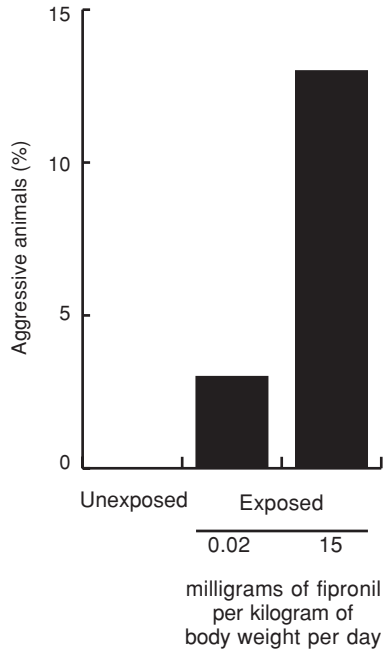
Effects on Hormones

Hormones are chemical messengers that regulate all biological processes, including the reproductive system.[16] Laboratory studies indicate that fipronil and commercial fipronil products disrupt the normal functions of two types of hormones: thyroid hormones and sex hormones.[17,18]

According to EPA, fipronil caused "dramatic alterations in thyroid function"[17] in the study mentioned above ("Neurotoxicity in Laboratory Animals"). In this study, levels of thyroid stimulating hormone in rats fed fipronil were more than double those in unexposed rats. The increases occurred at the two highest dose levels tested. In addition, levels of thyroxine were "dramatically reduced"[17] in rats fed fipronil. Thyroxine is a thyroid hormone that regulates the body's metabolic rate.[19] This decrease occurred at all dose levels tested.[17]

Scientists at the Universidade Federal do Paraná (Brazil) studied the effects on sex hormones of Frontline

Figure 2
Increase in Aggressive Behavior



Source: U.S. EPA. 1994. Data evaluation report: Combined chronic toxicity/ carcinogenicity/rats (83-5). MRID No. 429186-48. May 12, p. 11.

Fipronil increases the incidence of aggressive behavior in laboratory animals.

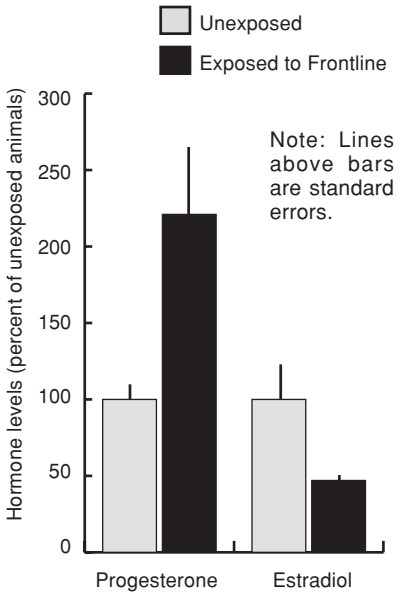
"INERT" INGREDIENTS

Inert ingredients in commercial fipronil products, with examples of their hazards, include the following:

- **Attapulgite clay**[1] (fibers longer than 5 micrometers) is classified as a carcinogen by the International Agency for Research on Cancer.[2]
- **Butylhydroxyanisole**[3] caused genetic damage and tumors in laboratory tests.[4]
- **Butylhydroxy toluene**[3] caused genetic damage and tumors in laboratory tests.[5]
- **Polyvinylpyrrolidone**[3] caused liver and ovarian tumors in laboratory tests.[6]
- **1,2 Polypropylene glycol**[1] caused genetic damage and reduced fertility in laboratory tests.[7]

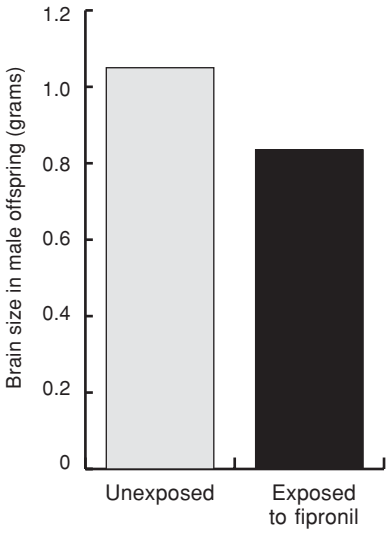
1. BASF Corporation. 2003. Material safety data sheet: Regent® 4 SC insecticide. www.cdms.net.
2. International Agency for Research on Cancer. 1997. Palygorskite (attapulgite). http://www-cie.airc.fr/htdocs/monographs/vol68/palygor.htm.
3. Merial Limited. 2001. Material safety data sheet: Frontline® TopspotTM. Iselin, NJ.
4. National Institute for Occupational Safety and Health. 2004. RTECS: Phenol, (1,1 - dimethylethyl) - 4 - methoxy -. www.cdc.gov/niosh/rtecs/sl1dada8.html.
5. National Institute for Occupational Safety and Health. 2004. RTECS: p - Cresol, 2,6 - di - tert - butyl. www.cdc.gov/niosh/rtecs/go7829b8.html.
6. National Institute for Occupational Safety and Health. 1997. RTECS: Poly (1 - vinyl - 2 - pyrrolidinone) Hueper's polymer No. 1. www.cdc.gov/niosh/rtecs/tr7c8300.html.
7. National Institute for Occupational Safety and Health. 2003. RTECS: 1,2-Propanediol. www.cdc.gov/niosh/rtecs/ty1e8480.html.

Figure 3
Ability to Disrupt Normal Hormone Function



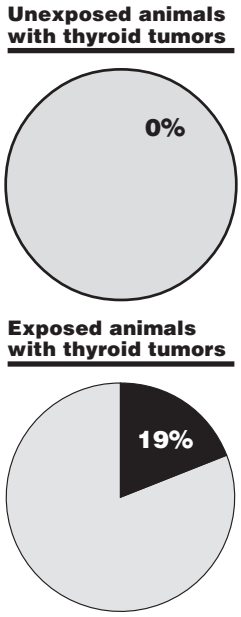
Source: Ohi, M. et al. 2004. Reproductive adverse effects of fipronil in Wistar rats. *Toxicol. Lett.* 146:121-127.

Figure 4
Ability to Disrupt Reproduction



Source: U.S. EPA. 1997. Data evaluation record: Developmental neurotoxicity study - rat; OPPTS 870.6300. Washington, D.C., June 9.

Figure 5
Ability to Cause Cancer



Source: U.S. EPA. 1994. Data evaluation report: Combined chronic toxicity/ carcinogenicity/rats (83-5). MRID No. 429186-48. May 12, p. 31.

Fipronil and fipronil-containing insecticides caused significant effects in tests with laboratory animals. These include disruption of normal hormone levels, effects on the developing brain, and thyroid tumors.

(a fipronil flea control product). They applied a single dose equivalent to a typical pet application to the skin of rats. They found that Frontline caused levels of progesterone to double and levels of estradiol to decrease to half the levels in unexposed rats.[18] (See Figure 3.) Progesterone is a hormone with pregnancy-related functions and estradiol is a hormone important in the development and maintenance of the female reproductive system.[19]

Effects on Reproduction

Frontline and fipronil also disrupt reproduction and development.

In the study mentioned in the preceding paragraph, a single dose of Frontline approximately doubled the time between periods of estrus in female rats.[18] (Estrus describes the time when a female is able to conceive; in many mammals this occurs in cycles.[19]) Higher doses of Frontline also reduced the number of female rats who were able to become pregnant following mating.[18]

Studies conducted as part of fipronil's registration process also documented effects on reproduction. Offspring of rats fed fipronil during pregnancy were smaller than offspring of unexposed rats. In addition, male offspring from exposed mothers took longer than offspring of unexposed mothers to mature sexually. These effects occurred at all but the lowest dose level tested. In another study, fipronil reduced litter size, fertility, and the survival of offspring. These effects occurred at the highest dose level tested.[20]

When pesticides are toxic to the nervous system, exposure during pregnancy might damage the developing nervous system of the unborn child. The first experiment mentioned in the preceding paragraph was designed to test for this kind of effect. It showed that the offspring of rats exposed to fipronil had smaller brains than the offspring of unexposed rats. (See Figure 4.) In addition, the fipronil exposure caused a variety of behavioral changes. All of these effects occurred at the highest dose level tested.[21,22]

Ability to Cause Cancer (Carcinogenicity)

EPA classified fipronil as a "possible human carcinogen" (Group C) in 1997.[23]

This classification is based on a study sponsored by a fipronil manufacturer. In this study, rats that were fed fipronil developed benign and malignant thyroid tumors. These tumors did not occur in unexposed animals.[23] (See Figure 5.)

Toxicity of Fipronil's Breakdown Products

When fipronil is exposed to light it can break down into a molecule called MB46513[24] or fipronil-desulfinyl.[25]

According to EPA, this breakdown product is about 10 times more toxic than fipronil itself. EPA bases this estimate on tests of acute toxicity, longer-term exposures, and a test of its ability to disrupt normal development. Fipronil-desulfinyl is also more easily absorbed through the skin than is fipronil.[24] (See Figures 6 and 7.) All of these tests were sponsored by a fipronil manufacturer.

Exposure from Flea Treatments

Flea treatments with fipronil commonly involve applying a small amount of insecticide to the nape of a pet's neck. The fipronil then binds to fatty material in the skin and hair cells where it is slowly released and spreads throughout the animal's skin and fur. Scientists at Murray State University studied the potential for veterinarians, groomers, and pet owners to be exposed to fipronil following a flea treatment. They found, during the first month after treatment, that petting an animal transferred fipronil from the animal to the person doing the petting. The amount of fipronil transferred was greatest one day after treatment. The researchers concluded that "repeated exposure to such contamination can pose human health risks."[26]

Fipronil on treated pets persists for at least 56 days following treatment according to pharmacologists working for a fipronil manufacturer.[27]

Persistence in Soil

According to a review of fipronil's environmental fate conducted by researchers from the University of Greenwich and a group of other United Kingdom research institutes, fipronil is "persistent"[28] in soil. As with most pesticides, fipronil's persistence varies dramatically depending on the specific conditions of the application site. The U.K. researchers reviewed studies showing that fipronil's half-life (the time required for half of the amount applied to break down or move away from the treatment area) varies from 2 weeks to 7 months, with half-lives in most soils greater than 2 months.[28]

Scientists from Australia's Commonwealth Scientific and Industrial Research Organisation studied persistence of the fipronil termiticide product Termidor and found that its half-life was over 4 months. Half-life of what the researchers called the "total toxic component" (fipronil and its breakdown products) was about 6 months.[29]

Water Contamination

Fipronil was not included in the National Water-Quality Assessment Program conducted by the U.S. Geological Survey (USGS).[30] This means that there is no systematic information about how often fipronil contaminates rivers and streams in the U.S. However, USGS did conduct a special monitoring program that measured fipronil contamination in a river basin in Louisiana, where the insecticide has been widely used to treat rice seed. Fipronil and four breakdown products were commonly found, and concentrations were highest in March and April. At the same sites, fipronil breakdown products were frequently found in river sediment.[31,32] USGS has also found fipronil in an urban stream in Seattle, Washington.[33]

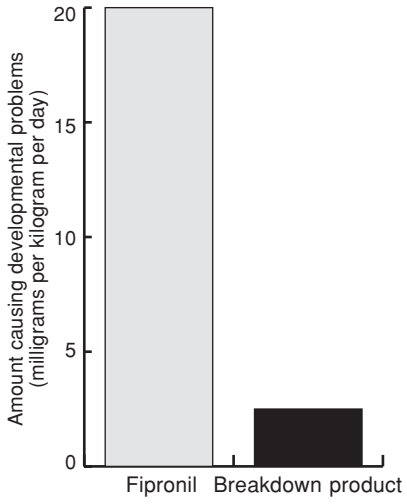
Effects on Birds

EPA classifies fipronil as "highly toxic" or "very highly toxic" to certain kinds of birds. According to tests sponsored by fipronil's manufacturer, small amounts of fipronil kill northern bobwhite quail, red-legged partridges, and pheasants.[34] Symptoms of poisoning include subdued behavior, unsteadiness, lethargy, diarrhea, and anorexia.[35-37] A fipronil breakdown product is more toxic than fipronil to birds.[34]

Effects on Lizards

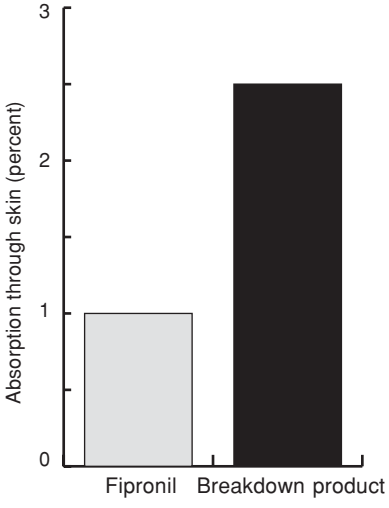
Fipronil has "high toxicity"[38] to lizards, according to a study conducted by scientists from the Universität Basel (Switzerland) and the Centre do Lutte Antiacridienne (Mauritania). They fed fipronil-contaminated prey to fringe-toed lizards and found that small amounts (the prey contained 30 micrograms of fipronil per gram of lizard body weight) killed almost 2/3 of the

Figure 6
Toxicity of a Fipronil Breakdown Product



Source: U.S. EPA. Office of Prevention, Pesticide and Toxic Substances. 1998. Fipronil for use on rice (Regent®, Icon®) and pets (Frontline®). HED risk assessment. Washington, D.C., May 22. p. 40.

Figure 7
Absorption of Fipronil and its Breakdown Product by Skin



Source: U.S. EPA. Office of Prevention, Pesticide and Toxic Substances. 1998. Fipronil for use on rice (Regent®, Icon®) and pets (Frontline®). HED risk assessment. Washington, D.C., May 22. Pp. 26-27.

A breakdown product of fipronil is about ten times more toxic than fipronil itself, and is more easily absorbed through the skin.

lizards and caused reduced feeding and weight loss in the survivors.[38] The lead researcher in this study also studied a locust control program in Madagascar. Fipronil locust treatments resulted in a "significant decline"[39] in populations of two native lizards.[39]

Effects on Fish

Low concentrations of fipronil kill most species of fish that have been tested. According to EPA, fipronil is "very highly toxic to the sunfish" and "highly toxic" to rainbow trout and sheepshead minnows.[2] Fipronil has a similarly high toxicity to carp.[40] Less than 1 part per million of fipronil kills all of these species. Fipronil is toxic enough to fish that fish were killed when "a dog treated with Frontline jumped into a pond of gold fish."[13]

A fipronil breakdown product is between 3 and 6 times more toxic to fish than fipronil.[2]

Fipronil is particularly toxic to juvenile fish. In a study sponsored by a fipronil manufacturer, a concentration of 15 parts per billion (ppb) reduced growth of larval trout.[2]

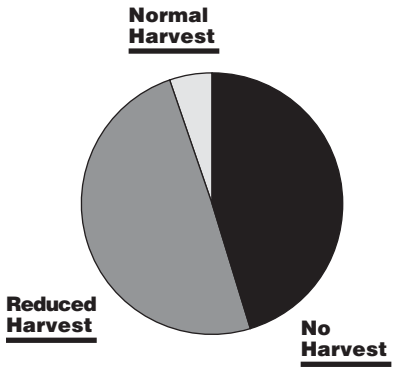
In addition, fipronil bioaccumulates in fish. This means that the concentration of fipronil in fish in contaminated water is higher than the concentration of fipronil in the water in which they live. In a study sponsored by a fipronil manufacturer, the bioconcentration factor (the ratio of the concentration in a fish to the water concentration) was over 300.[2]

Effects on Crawfish

In Louisiana, where crawfish and rice are raised in the same or nearby fields, fipronil treatment of rice seeds caused "catastrophic loss"[41] of crawfish. Based on a survey of crawfish farmers in 2000, Louisiana State University reported that only 5 percent of rice field/crawfish ponds where fipronil had been used produced normal crawfish harvests.[41] (See Figure 8.)

In a laboratory study conducted by scientists at the University of California, Riverside, the University of Mississippi, and Rice University, minute amounts of fipronil (less than 20 ppb) killed crawfish. Even smaller amounts (less than 16 ppb) of two fipronil breakdown products also killed crawfish.[42]

Figure 8
Effect of Fipronil Treatments on Harvest of Crawfish from Rice Fields



Source: Avault, J.W. 2001. Research report - Catastrophic loss of pond-raised crawfish attributed to rice insecticide. *Aquaculture Magazine* 26: 45-49.

Rice farmers using fipronil-treated seed caused catastrophic losses in Louisiana's crawfish industry.

Effects on Shrimp

Extremely low concentrations of fipronil also kill shrimp. In laboratory studies, concentrations of less than one ppb kill grass shrimp.[43] Other species of shrimp are also killed by low concentrations.[44-46]

Researchers from the National Oceanic and Atmospheric Administration and the University of South Carolina showed that fipronil, at about half the concentration that caused mortality (0.15 ppb), changed the sex ratio of shrimp populations, increasing the number of males.[45]

Fipronil reduces the growth of shrimp at even lower concentrations. A study sponsored by a fipronil manufacturer found that concentrations as low as 5 parts per trillion (.005 ppb) reduced growth of mysid shrimp.[47]

Effects on Bees

Minute amounts of fipronil (0.004-0.005 micrograms per bee) kill honey bees.[48] Effects on bees' foraging have occurred at even lower exposures.[49] Fipronil is also toxic to bumblebees.[50]

Effects on Beneficial Organisms

Fipronil is toxic to a variety of beneficial organisms, a phrase used to describe organisms that are important in controlling agricultural pests. These include several bugs,[50-52] a mite,[50] and a lacewing.[53]

Effects on Other Animals

The effects of fipronil exposure on the ability of copepods to successfully reproduce have been intensively studied. Copepods are small aquatic animals that are "the most abundant arthropods on earth."[54] They are an important part of the food web in estuaries and the ocean. For example, they are "often the primary prey item for juvenile fishes"[54] in estuaries.

In a series of studies, researchers from the University of South Carolina and the University of Maryland found that fipronil exposure to concentrations of less than 1 ppb caused delayed sexual development, halted egg production,[55] and increased the number of infertile males.[54] Looking more broadly at successful reproduction, the researchers found that a concentration of 0.16 ppb caused the size of a copepod population to decline[55] and a concentration of .065 ppb reduced the number of offspring produced by copepods living in fipronil-contaminated sediment.[56] Fipronil breakdown products caused reproductive problems at similar concentrations.[56]

Resistance

Although fipronil is a relatively new insecticide, four species (the Asiatic rice borer, the house fly, the diamondback moth, and a mosquito) have developed resistance to it.[57,58] Resistance is the term used to describe a reduction in the susceptibility of an insect population to an insecticide.[59]

Fipronil resistance can develop quickly. In Taiwan, fipronil was first used in 1996 and the diamondback moth had developed resistance within two years. After five years of use, the amount of fipronil required to kill diamondback moths in Taiwan had increased 100-fold.[60]

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