

# Comprehensive Review on Fipronil: A Detailed Exploration of Its Effect and Mechanisms

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## ABSTRACT

**Fipronil is a widely used insecticide known for its effectiveness against a broad spectrum of pests. This review examines its or Ignis, chemical properties, uses, and its significant impacts on health and the environment. While highly effective, its persistence in ecosystems and potential toxicity to non-target species, including humans, raises important concerns. The author presents a comprehensive analysis highlighting the molecular mechanisms behind its effects, especially hepatotoxicity, and explores protective strategies, such as antioxidant interventions. The aim of the review is to balance the utility of fipronil with safety, advocating for informed usage and further research.**

**Keywords: Fipronil, Histology, Immunohistochemical, Histomorphological Alteration, Biochemical Analysis.**

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## INTRODUCTION

Insecticides have transformed pest management, ensured higher agricultural yields, and controlled disease vectors, among these, fipronil has stood out since its introduction in the 1990s, according to researchers, its ability to disrupt gamma-aminobutyric acid (GABA)-gated chloride channels in pests offers precise action against insects while sparing mammals due to species-specific receptor differences (Tingle *et al.*, 2003). The authors note that this selectivity has made fipronil a cornerstone in managing pests like termites, fleas, and agricultural threats such as rice water weevils (Sanchez *et al.*, 2003).

Fipronil's widespread presence and potential for contamination have been underscored by its detection in diverse environmental samples, including surface water, urban waterways, rural rivers, agricultural runoff, indoor and outdoor dust, soil, and wastewater effluent (Budd *et al.*, 2015). Fipronil has emerged as a widely used insecticide, providing a solution to resistance and health concerns associated with traditional pesticide groups (Bonmatin *et al.*, 2015).

### Discovery

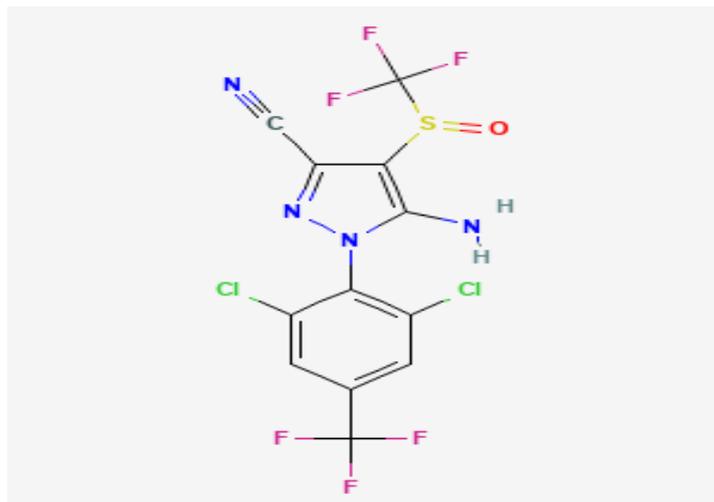
Fipronil was developed by Rhône-Poulenc Agro in the early 1990s and approved by the United States Environmental Protection Agency (USEPA) in 1996 (Chiovarou and Siewicki, 2008). The researchers designed it as a safer alternative to organophosphates and carbamates, introducing a new mode of action that targets GABA-gated chloride channels, a mechanism distinct from older insecticides (Narahashiet *et al.*, 2010). According to the scientists, this specificity minimizes fipronil's impact on mammals, offering a solution to pesticide resistance and toxicity issues (Hainzl and Casida, 1996).

Fipronil's adoption has spanned agriculture, veterinary medicine, and public health. In agriculture, researchers have utilized it to combat pests that damage staples like rice and maize. Veterinarians have employed it as a popular topical treatment for fleas and ticks in pets. Public health initiatives have also utilized it against cockroaches and other vectors (Gupta and Anadon, 2018). However, scientists have noted that its environmental persistence and toxic metabolites, such as fipronil sulfone, pose ecological challenges (Caboni *et al.*, 2003). Ongoing research aims to unravel its long-term impacts, focusing on environmental accumulation and mitigation strategies. Studies emphasize the importance of informed application to reduce risks to non-target organisms (Chiovarou and Siewicki, 2008).

### Structure and Properties

Fipronil, with chemical formula (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(trifluoromethyl)sulfinyl)pyrazole-3-carbonitrile), is a white crystalline powder with a mild mold-like odor (Tingle *et al.*, 2003). It has a molecular formula of C<sub>12</sub>H<sub>4</sub>Cl<sub>2</sub>F<sub>6</sub>N<sub>4</sub>OS with molecular weight of 437.15 g/mol and a melting point of 200-201 °C. Sparingly soluble in water 1.9 mg/L (pH 5), 2.4 mg/L (pH 9), 1.9 mg/L (distilled), all at 20 °C (Thangamani *et al.*,

2018). This property underpins fipronil's efficacy and bioaccumulation potential, necessitating that researchers and regulators implement careful management strategies to mitigate environmental and health risks (Bhartiya *et al.*, 2020).



**Fig 1: Chemical structure of Fipronil (<http://pubchem.ncbi.nlm.nih.gov>)**

### General Toxicity

Research conducted in murine and rodent models has shown that oral fipronil administration induces a range of toxicological effects, encompassing neurotoxicity, hepatotoxicity, reproductive toxicity, and endocrine disruption (Ohi *et al.*, 2004; Leghaitet *et al.*, 2009; De Oliveira *et al.*, 2012).

The lipophilic properties of fipronil enable its accumulation in tissues with high lipid content, including the brain, leading to prolonged retention (Stafford *et al.*, 2018). Ingestion of fipronil by humans can lead to a range of symptoms, including sweating, nausea, vomiting, headache, abdominal pain, dizziness, agitation, weakness, and seizures.

Fortunately, these effects are generally reversible and self-resolving (Mohamed *et al.*, 2004). According to the US Environmental Protection Agency's Ecological Risk Assessment Report, fipronil exhibits severe toxicity to a wide range of species, encompassing birds, mammals, freshwater fish, invertebrates, algae, and vascular plants (USEPA 2005).

### Mode of action

Oxidative stress-mediated mode of action proposed for fipronil (FIP). Increased generation of ROS, as well as an alteration in antioxidant status, may induce lipid, protein and DNA oxidation, leading to various toxicities and apoptosis via the ERK, p38, JNK, AKT, Ca<sup>2+</sup>, mitochondrial apoptosis, and CAR/PXR pathways.

### Uses of Fipronil

Fipronil is a versatile insecticide with a wide range of applications. In agriculture, it is used to control various pests that damage crops, such as rice, maize, and sugarcane. Fipronil is effective against insects like stem borers, leaf folders, and plant hoppers, which can significantly reduce crop yields.

Its use in agriculture has been instrumental in increasing food production and reducing economic losses due to pest damage (Sanchez *et al.*, 2013). In veterinary medicine, fipronil is used to control external parasites like fleas, ticks, and lice on pets. It is available in various formulations, including spot-on treatments, sprays, and shampoos. Fipronil works by killing these parasites, thereby preventing the transmission of diseases like typhus, tapeworms, and flea allergy dermatitis (Gupta and Anadon 2018).

### Effects of Fipronil

General symptoms of fipronil exposure are similar in rats and humans and include increased excitability, headache, dizziness, seizures, reduced food consumption, nausea and vomiting in humans (Mohamed *et al.*, (2004). In addition, it was found to exert genotoxic and mutagenic effects in mice and humans (De Oliveira *et al.*, 2010); Çelik *et al.*, 2014).

### **Morphological and Anatomical study of organs**

Studies have shown that exposure to fipronil results in liver damage, marked by hepatocyte necrosis, inflammation, and fibrosis (Bhartiya *et al.*, 2020). Researchers have found that fipronil exposure disrupts the liver's lobular structure and sinusoidal network, leading to impaired liver function (Kumar *et al.*, 2018). According to (Badgujar *et al.*, 2015), the extent of damage caused by fipronil exposure correlates with the dosage and duration, highlighting the importance of controlled application.

### **Body weight**

According to (Chaguret *et al.*, 2016), animal studies have demonstrated that chronic fipronil exposure leads to reduced body weight gain, likely resulting from systemic metabolic disturbances and oxidative stress. For instance, Refaie *et al.*, (2021) found a statistically significant decrease in body weight gain in rats exposed to fipronil. Similarly, Elgawish *et al.*, (2018) reported a significant decrease in body weight in male rats exposed to fipronil at a dose of 9.7 mg/kg. Additionally, Mossa *et al.*, (2015) observed a slight decrease in body weight after 45 days of exposure to fipronil (FPN) at concentrations of 1 and 10 mg/L in male albino rats, these findings suggest that fipronil exposure may have a negative impact on overall health and nutritional status, potentially leading to reduced body weight gain.

### **Organ weight**

Refaie *et al.*, (2021) reported a significant increase in relative liver weight in animals exposed to fipronil, indicating potential liver hypertrophy and increased risk of liver damage or dysfunction. Similar findings were reported by Elgawish *et al.*, (2018), who found that rats administered fipronil (FPN) at a dose of 9.7 mg/kg had a significant increase in relative liver weight in male rats. Mossa *et al.*, (2015) also observed significant alterations in liver weights in rats exposed to 10 mg/L of fipronil, however, the effects of fipronil on liver weight appear to be dose-dependent exposed to 1 mg/L of FPN exhibited only slight changes in relative liver weight, suggesting that lower doses of fipronil may have less pronounced effects on liver weight.

### **Histomorphological Alteration in Liver**

According to Bhartiya *et al.*, (2020), fipronil exposure has been found to cause hepatocyte necrosis, characterized by pyknosis, karyolysis, and cytoplasmic vacuolation. Researchers, including Gupta *et al.*, (2019), have discovered that fipronil induces inflammatory responses in the liver, marked by infiltration of neutrophils and macrophages. Studies by Kumar *et al.*, 2018, have demonstrated that chronic fipronil exposure leads to liver fibrosis, characterized by deposition of collagen fibers and formation of fibrotic nodules. As reported by Singh *et al.*, 2019, fipronil exposure has been shown to cause steatosis, characterized by accumulation of lipid droplets in hepatocytes. According to Chaguret *et al.*, (2016), fipronil has been found to induce apoptosis in hepatocytes, marked by chromatin condensation, DNA fragmentation, and formation of apoptotic bodies.

### **Histological alteration**

The hepatotoxic effects of fipronil have been consistently demonstrated across various studies. Abdel-Daim *et al.*, (2018) reported severe liver damage characterized by portal vein congestion, hydropic degeneration, and necrosis. Similarly, Elgawish *et al.*, (2018) and Wasef *et al.*, (2021) observed significant liver damage, including portal vein congestion, hydropic degeneration, and necrosis, in rats treated with fipronil. Furthermore, Ardeshir *et al.*, (2024) found that grass carp exposed to fipronil suffered from notable hepatological damage, including steatosis and vein dilatation, which is consistent with the findings of Bal *et al.*, (2021) who reported microsteatosis and hypertrophy of hepatocytes in mice administered fipronil. Abou-Zeid *et al.*, (2020) also observed congestion of the central vein with infiltration of inflammatory cells, ballooning degeneration of hepatocytes, and areas of coagulative necrosis. Fredianelli *et al.*, (2019) found that exposure to fipronil at concentrations of 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.8 mg L<sup>-1</sup> caused significant liver damage in silver catfish, characterized by lesions such as steatosis, nuclear degeneration, and tissue necrosis. Mossa *et al.*, (2015) investigated the effects of sub-chronic exposure to fipronil (FPN) on the liver and kidney of male rats, exposing them to FPN in drinking water at concentrations of 0.1, 1, and 10 mg/L.

The results revealed severe histopathological alterations in the liver, including degeneration, infiltration, and inflammatory cells, with high-dose exposure (10 mg/L) causing the most severe damage, while medium-dose exposure (1 mg/L) resulted in degeneration of hepatocytes and portal infiltration, and low-dose exposure (0.1 mg/L) caused mild alterations. Elazabet *et al.*, (2021) observed that rats treated with FPN (19.4 mg/kg) exhibited significant liver damage. This

included disorganization in their hepatic cords, with the formation of broad fibrous septa that separated the hepatic lobules. Additionally, there was evidence of leukocytic cell infiltration, congested blood vessels, and dilated lymphatics, all indicating substantial hepatic alterations. In the study by Anber *et al.*, (2021), adult albino mice were used to assess the effects of fipronil (40, 80, 160, and 320 mg/kg body weight), leading to observable liver damage, including a reduction in hepatic vacuolar changes, mild inflammatory cell infiltration, and moderate necrosis of hepatocytes.

### Enzymes Tests

Studies by Gupta *et al.*, 2019; Kumar *et al.*, (2018), have demonstrated that fipronil exposure increases the levels of ALT and AST in rat and mouse liver, respectively, indicating liver damage. Furthermore, research by Bhartiya *et al.*, (2020); Chagaret *et al.*, (2016), has shown that fipronil exposure decreases the levels of GST and CAT in rat liver, indicating oxidative stress. Exposure to FPN at different concentrations resulted in altered serum enzyme activities. Specifically, exposure to 1 and 10 mg/L of FPN for 45 days resulted in a significant elevation of serum enzyme activities, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). In contrast, exposure to a lower concentration of FPN (0.1 mg/L) had a more selective effect, significantly increasing the activity of ALT, while having no significant impact on the activities of AST, ALP, and LDH as reported by Mossa *et al.*, (2015).

Kartheek and David (2018) reported significant increases in liver enzyme levels following 90-day exposure to Fipronil, Alanine aminotransferase (ALT) activity rose by 304.02%, 82.46%, and 46.39% in the high (32.33mg) medium (12.12mg), and low (6.46 mg) per kg body weight/day respectively, A similar trend was observed for alkaline phosphatase (ALP) levels, with percent increases of 165.08%, 124.42%, and 10.64% in the high, medium, and low-dose groups, respectively. The study by Refaie *et al.* (2021) found elevated activity levels of serum enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), in animals exposed to fipronil, it may cause liver damage or dysfunction, leading to increased activity levels of these serum enzymes. Additionally, Abdel-Daim *et al.*, (2018) reported that biochemical analysis of the serum revealed substantial increases in liver enzymes AST, ALT, ALP, LDH and cholesterol levels, these enzyme results suggest that fipronil exposure impaired liver and kidney function, leading to disruptions in lipid metabolism and potential systemic toxicity. Al-Janabi *et al.*, (2023) found that sub-chronic exposure to fipronil (20 mg/kg), nano-fipronil (10 mg/kg and 20 mg/kg) caused liver damage in rats, indicated by significant increases in serum enzymes AST, ALT, and ALP, as well as elevated levels of total protein.

According to Abouelgharet *et al.*, (2019), exposure to fipronil at doses of 1.43, 2.87, and 4.78 mg/kg led to a significant increase in liver enzyme activities, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Notably, the increase in ALP activity was dose-dependent, with higher doses of fipronil corresponding to greater increases in enzyme activity. A study by Ardeshir *et al.*, (2024) found that exposure to fipronil at concentrations of 3, 6, and 10 µg L<sup>-1</sup> had significant biochemical effects on grass carp, The results showed that EROD activity increased in a dose-dependent manner, while GST activity increased in a time-dependent manner. Additionally, the MDA content increased in both a time- and dose-dependent manner, indicating oxidative stress and lipid peroxidation. Akhila and Vijaya (2020) found that fipronil exposure (9.5 mg/kg and 95 mg/kg) caused significant increases in liver enzymes (AAT, ALT, SDH, and LDH) in Swiss albino mice, indicating hepatotoxic effects.

### Biochemical analysis

According to Tomizawa *et al.*, (2005), fipronil has been found to inhibit the activity of cytochrome P450 enzymes in the liver, leading to changes in the metabolism of various compounds. Furthermore, research conducted by Singh *et al.*, (2012) revealed that exposure to fipronil results in increased oxidative stress and lipid peroxidation in the liver, leading to cellular damage. Joshi *et al.*, (2013) also reported that fipronil depletion of glutathione levels in the liver compromises the antioxidant defenses of the cell.

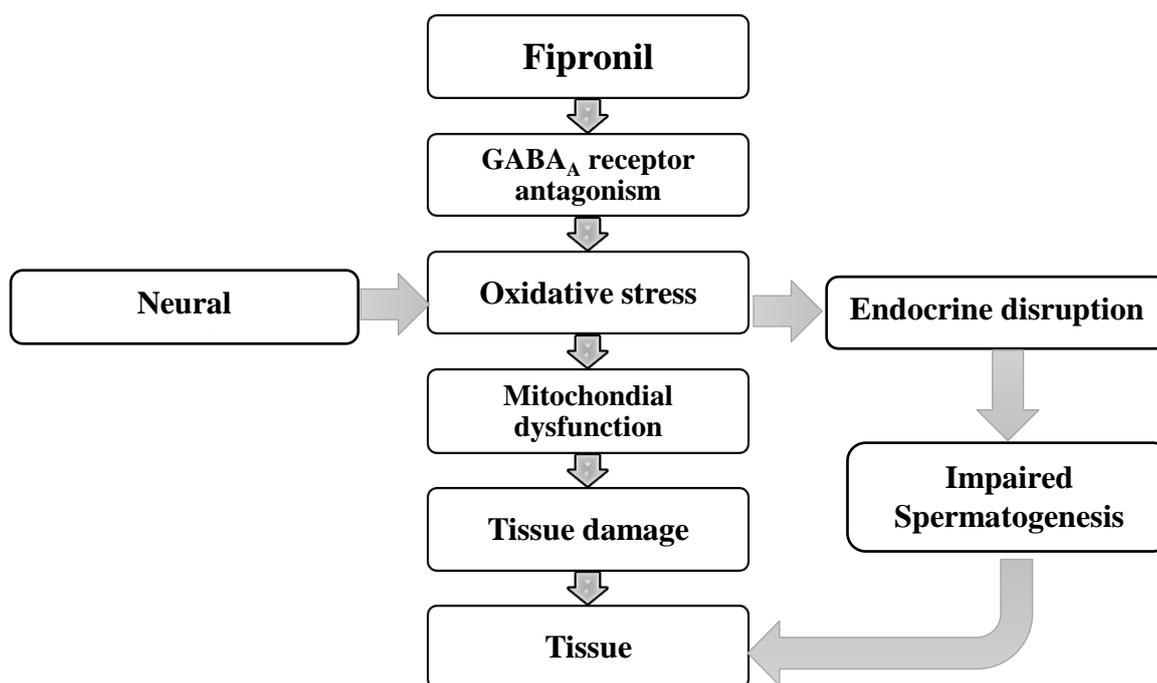
Moreover, Bhaskar *et al.*, (2016) observed changes in liver enzyme activity, including increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), following fipronil exposure. These findings collectively indicate that fipronil induces significant biochemical changes in the liver, highlighting the importance of further research into its hepatotoxic effects.

### Immunohistochemical Alteration

Studies have shown that fipronil exposure leads to immunohistochemical alterations in the liver, indicating hepatotoxicity. The work of Gupta *et al.*, (2019), revealed that fipronil exposure upregulates the expression of TNF- $\alpha$  and IL-1 $\beta$  in rat liver, indicating an inflammatory response. Furthermore, Kumar *et al.*,(2019), observed that fipronil exposure increases the expression of COX-2 and iNOS in mouse liver, indicating oxidative stress. Treatment with Fipronil (FIP) resulted in a significant upregulation of caspase-3 activity (Wasef *et al.*, 2021)

### Mechanism of Fipronil in Animal

Studies have shown that fipronil's binding to GABA-gated chloride channels inhibits the influx of chloride ions into the neuron (Bhartiya *et al.*, 2020). The inhibition of GABA-gated chloride channels increases neuronal excitability, resulting in hyperexcitation (Chagur *et al.*, 2016). Researchers have found that the increased neuronal excitability activates glutamate receptors, leading to an influx of calcium ions into the neuron (Singh *et al.*, 2019). The increased intracellular calcium levels lead to neurodegeneration, characterized by neuronal damage and death (Gupta *et al.*, 2019).



**Fig2: Fipronil's Mode of Action: GABA<sub>A</sub> Receptor Blockade Leading to Neurotoxicity**

### CONCLUSION

Fipronil exposure causes significant liver damage, characterized by oxidative stress, inflammation, mitochondrial dysfunction, and ultrastructural changes. These findings indicate that fipronil poses a substantial risk to liver health, highlighting the need for caution and further research. This study ultrastructurally analyzed the livers of mice exposed to various doses of Fipronil to identify the toxic effects on the organ. Furthermore, the research demonstrated potential impairments caused by Fipronil in non-target organisms under artificial conditions, complementing existing knowledge of the pesticide's metabolic pathways.

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