Effect of fipronil on kidney: a review

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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 origins, 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. This comprehensive analysis highlights the molecular mechanisms behind its effects, especially nephrotoxicity and explores protective strategies, such as antioxidant interventions. The aim of this review is to balance its utility with safety, advocating for informed usage and further research.

***Key words*:** Fipronil, kidney, nephrotoxicity, insecticide

I. INTRODUCTION

Fipronil, a phenylpyrazole insecticide, disrupts the central nervous systems of insects by targeting gamma-aminobutyric acid (GABA)-regulated chloride channels (Tingle *et al*., 2003). Due to its effectiveness, it is widely applied in agriculture, veterinary medicine, and public health (Gupta and Anadon, 2018). Approved by the (USEPA, 1996) U.S. Environmental Protection Agency as a replacement for organophosphate insecticides, fipronil has since raised concerns about its potential risks to human health and the environment (Chiovarou and Siewicki, 2008).

Exposure to fipronil induces oxidative stress by increasing reactive oxygen species (ROS) and reducing the activity of antioxidant enzymes. This oxidative imbalance leads to mitochondrial damage and triggers apoptosis (Mossa *et al*., 2015; Abdel-Mobdy *et al*., 2023; Uzunhisarcikli *et al*., 2023). Fipronil also causes liver damage, evidenced by elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are markers of hepatic injury and disrupts cytochrome P450 enzymes, contributing to hepatotoxicity (Abou-Zeid *et al*., 2021; Mossa *et al*., 2015).

As a neurotoxin, fipronil interferes with GABAergic signaling, leading to neuronal degeneration, motor deficits, cognitive impairments and kidney damage, including tubular degeneration and inflammation (Bharatiya *et al*., 2020; Sakr *et al*., 2022; Uzunhisarcikli *et al*., 2023).

Fipronil acts as an endocrine disruptor by interfering with the hypothalamic-pituitary-thyroid axis, potentially leading to hypothyroidism, fertility issues and as a possible human carcinogen, with chronic exposure associated with liver and thyroid tumors (USEPA, 1996; Chiovarou and Siewicki, 2008). It also influences immune responses by increasing inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Uzunhisarcikli *et al*., 2023).

Human exposure to fipronil can cause acute symptoms, including headaches, seizures, and respiratory or skin irritation. Long-term exposure may increase the risk of neurodegenerative diseases and reproductive health issues (Hainzl *et al.*, 1998; Mossa *et al*., 2015). The fipronil's oxidative stress mechanisms particularly affect the liver, kidneys, and brain, impairing antioxidant defenses and causing tissue damage (Banerjee *et al*., 2001; Bebe and Panemangalore, 2005).

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). Designed as a safer alternative to organophosphates and carbamates, it introduced a new mode of action targeting GABA-gated chloride channels, a mechanism distinct from older insecticides (Narahashi *et al*., 2010). This specificity minimizes its impact on mammals, offering a solution to pesticide resistance and toxicity issues (Hainzl and Casida, 1996).

Its adoption spanned agriculture, veterinary medicine, and public health. In agriculture, it combats pests that damage staples like rice and maize. In veterinary contexts, it is a popular topical treatment for fleas and ticks in pets. Public health initiatives employ it against cockroaches and other vectors (Gupta and Anadon, 2018). However, its environmental persistence and toxic metabolites, such as fipronil sulfone, pose ecological challenges (Caboni *et al*., 2003).

Research continues 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 the chemical formula (5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole), is a white crystalline powder with a mild mold-like odor (Tomlin, 2006). It has a molecular weight of 473.2 g/mol and a melting point of 200–201°C. Sparingly soluble in water (1.9 mg/L at pH 5), it dissolves readily in organic solvents like toluene (3000 mg/L) and hexane (28 mg/L), highlighting its lipophilic characteristics (USEPA, 1996). This property underpins its efficacy and bioaccumulation potential, necessitating careful management to mitigate environmental and health risks (Bhartiya *et al*., 2020).

Uses

Fipronil's adaptability has made it indispensable across various zones. In agriculture, it protects crops from pests like rice water weevils, termites and rootworms through seed and soil treatments (Sanchez *et al*., 2003). Veterinary medicine benefits from its efficacy against fleas and ticks in pets, delivered through topical formulations (Gupta and Anadon, 2018). Its household applications include gel baits and liquid termiticides for controlling cockroaches and ants (New Pesticide Products, 2007).

II. MORPHOLOGICAL AND ANATOMICAL STUDY OF FIPRONIL AFFECTED ORGANS

Fipronil exposure has far-reaching implications for health, primarily driven by oxidative stress and disrupted antioxidant defenses. These effects manifest in structural and functional changes in key organs, including the kidneys, liver, and brain.

Weight Response

Fipronil has been shown to influence the body and organ weights of rats in varying ways. Studies by Badgujar *et al*., (2015) and Uzunhisarcikli *et al*., (2023) reported no significant changes in the overall body weight of rats. However, findings from Badgujar *et al*., (2015), Mossa *et al*., (2015), Noaishi and Abd Alhafez (2017) and Soliman *et al*., (2023) revealed a reduction in the relative weight of the kidneys and decrease in the overall body weight in exposed rats. In contrast, research by Abdelgadir *et al*., (2020) and Abdel-Mobdy *et al*., (2022) noted an increase in the body weight of rats following fipronil exposure.

Histopathological studies

Histopathological studies reveal that fipronil exposure causes significant damage to renal tissues. Observations include tubular degeneration, glomerular atrophy, and interstitial inflammation (Uzunhisarcikli *et al*., 2023). The extent of damage correlates with dosage and duration of exposure, emphasizing the need for controlled application (Badgujar *et al*., 2015). Fipronil-induced nephrotoxicity is marked by elevated blood urea nitrogen (BUN) and serum creatinine levels. Structural damage, such as tubular necrosis and glomerular shrinkage, underscores its toxic impact. Antioxidants like vitamins E and C show potential in mitigating these effects (Mossa *et al*., 2015; Badgujar *et al*., 2015).

Hormone analysis

Fipronil and its metabolites disrupt endocrine pathways, particularly the hypothalamic-pituitary-thyroid axis. Studies report reduced levels of thyroid hormones, including triiodothyronine (T3) and thyroxine (T4), indicating hypothyroidism (USEPA, 1996; Chiovarou and Siewicki, 2008).

Enzyme Tests

Exposure to fipronil inhibits antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while increasing lipid peroxidation markers such as malondialdehyde (MDA) (Mossa *et al*., 2015; Abdel-Daim and Abdeen, 2018).

Immunohistochemical Alteration

Immunohistochemical analyses reveal increased expression of caspase-3 in renal tissues, indicating heightened apoptotic activity in response to fipronil exposure (Sakr *et al*., 2022).

Reactive oxygen species

Fipronil's nephrotoxicity stems from its ability to generate reactive oxygen species (ROS), leading to oxidative stress and mitochondrial dysfunction. This cascade results in lipid peroxidation, protein oxidation, and DNA damage, culminating in renal cell apoptosis (Abdel-Daim *et al*., 2018). Elevated levels of renal biomarkers, such as creatinine and BUN, corroborate these findings (Sakr *et al*., 2022).

III. MECHANISM OF ACTION OF FIPRONIL

Fipronil inhibits $GABA_A$ receptors in rat dorsal root ganglion (DRG) neurons by reversibly blocking GABA-induced currents with an IC_{50} of 1.66 ± 0.18 μM. When pre-applied, fipronil suppresses GABA currents without channel activation, indicating its effect on GABA receptors in the closed state. For active receptors (co-application with GABA), the IC_{50} decreases to 1.12 ± 0.21 μM.The association and dissociation rates for the resting receptor are 673 ± 220 M^{-1} sec^{-1} and 0.018 ± 0.0035 sec^{-1}, with an equilibrium dissociation constant (K_d) of 27 μM. For active receptors, these values increase to 6600 ± 380 M^{-1} sec^{-1} and 0.11 ± 0.0054 sec^{-1}, with a K_d of 17 μM. This tenfold increase in rate constants for active receptors results in a lower K_d for fipronil when the channel is open. Single-channel recordings from rat DRG neurons for $GABA_A$ receptors indicated that fipronil prolongs the closed state while having little effect on the open state or burst duration. This decrease in channel opening frequency reduces the receptor activity (Ikeda *et al.,* 1999)

IV. CONCLUSION

Fipronil demonstrates the contrast of modern pesticides: highly effective yet fraught with risks. Its persistent and bio accumulative nature, coupled with its nephrotoxic and systemic effects, calls for careful application and stringent regulatory oversight. Promising mitigation strategies, including the use of antioxidants and natural extracts, offer hope for reducing its adverse impacts. Future research should focus on refining its usage and exploring safer alternatives to ensure sustainable pest management.

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