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ACUTE FIPRONIL SULFONE TOXICITY INDUCES MULTI-ORGAN HISTOPATHOLOGY IN MALE MICE: A COMPREHENSIVE HISTOMORPHOMETRIC ANALYSIS

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ABSTRACT: Fipronil sulfone is the predominant metabolite of the insecticide fipronil, produced via cytochrome P450 oxidation. It exhibits greater persistence and higher toxicity than its parent compound, yet its histopathological effects remain unexplored. To evaluate histopathological changes induced by acute fipronil sulfone exposure in male mice.

Sixteen adult male mice were divided into control (DMSO) and treated (100 mg/kg fipronil sulfone, intraperitoneal) groups (n=8). Liver, kidney, brain, testis, and seminal vesicles were processed for H&E, PAS, and Trichrome staining. Histomorphometric analysis was performed using ImageJ software. Fipronil sulfone caused significant testicular damage including reduced tubular diameter (168.32±7.54 vs. 212.45±8.67 µm), epithelial height (58.67±2.93 vs. 78.34±3.21 µm), tunica albuginea thickness (28.43±1.89 vs. 42.67±2.31 µm), and increased interstitial space (7.96±0.61 vs. 4.82±0.34 µm) and tubular lumen (72.56±3.78 vs. 45.23±2.45 µm). Seminal vesicles showed metaplasia and increased epithelial height (27.89±1.67 vs. 18.34±1.23 µm). Renal damage included reduced corpuscle (3187±142 vs. 4234±156 µm²) and glomerular area (1978±87 vs. 2845±98 µm²), increased Bowman's space (567±31 vs. 312±24 µm²), and PCT brush

border loss. Hepatic alterations showed increased pericentral degenerated hepatocytes (12.7±1.3 vs. 3.4±0.5 per field). Hippocampal neurodegeneration increased significantly (21.6±2.1 vs. 5.2±0.8 degenerated neurons per field). All changes were statistically significant ($p<0.05$).

This first comprehensive study demonstrates that acute fipronil sulfone exposure induces significant multi-organ histopathological damage in mice, highlighting the need for risk assessment of pesticide metabolites.

Keywords: *Fipronil sulfone, histopathology, testis, kidney, liver, hippocampus, neurotoxicity, nephrotoxicit*

1. INTRODUCTION

Metabolite toxicology has emerged as a critical scientific discipline that recognizes the often-overlooked reality that pesticide metabolites can exhibit greater environmental persistence and higher toxicity than their parent compounds [1]. This paradigm shift in toxicological assessment has significant implications for public health and environmental safety, as regulatory frameworks historically focused primarily on parent compounds while giving insufficient attention to their degradation products. The case of fipronil and its major metabolite fipronil sulfone exemplifies the importance of this emerging field, demonstrating how biotransformation can generate compounds with enhanced toxic potential. Fipronil is a broad-spectrum phenylpyrazole insecticide first developed by Rhône-Poulenc in 1987 and introduced to the global market in 1993 [2]. It was registered for use in the United States in 1996 and has since become one of the most widely used insecticides worldwide, accounting for approximately 10% of the global insecticide market [3]. The compound's chemical designation is 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile, with the molecular formula $C_{12}H_4Cl_2F_6N_4OS$ [4]. Fipronil's popularity stems from its high efficacy against a broad spectrum of insect pests including termites, ants, beetles, cockroaches, fleas, ticks, and weevils, coupled with its relatively low acute toxicity in mammals compared to older insecticide classes such as organophosphates and carbamates [5]. The primary mechanism of action of fipronil involves non-

competitive allosteric blockade of gamma-aminobutyric acid (GABA)-gated chloride channels in the insect central nervous system [6]. GABA is the principal inhibitory neurotransmitter in both invertebrates and vertebrates, and disruption of GABAergic signaling leads to neuronal hyperexcitation, paralysis, and death. Fipronil exhibits approximately 200-300-fold higher affinity for insect GABA receptors compared to mammalian receptors, which contributes to its selective toxicity [7]. However, this selectivity is not absolute, and concerns regarding mammalian toxicity have persisted since its introduction.

In the environment and within biological systems, fipronil undergoes several transformation pathways including oxidation, reduction, photolysis, and hydrolysis [8]. Among these, cytochrome P450-mediated oxidation represents the predominant metabolic pathway in mammals, yielding fipronil sulfone ($C_{12}H_4Cl_2F_6N_4O_2S$) as the major metabolite [9]. This biotransformation is primarily catalyzed by CYP3A4 isoenzymes in humans and rodents, converting the sulfinyl moiety of fipronil to a sulfonyl group [10]. The significance of this metabolic conversion cannot be overstated, as fipronil sulfone demonstrates markedly different toxicological properties compared to its parent compound.

Fipronil sulfone exhibits approximately 20-fold higher affinity for mammalian GABA receptors than fipronil itself, as demonstrated by electrophysiological studies on rat GABA receptors [11]. This enhanced receptor binding translates to greater neurotoxic potential. Furthermore, the metabolite shows 54-fold greater potency in reducing cell viability in human neuronal cell lines, with cytotoxicity mediated through oxidative stress mechanisms involving reactive oxygen species generation, mitochondrial dysfunction, and activation of apoptotic pathways [12]. The half-life of fipronil sulfone in mammalian systems is considerably longer than that of fipronil, with estimates ranging from 150-245 hours in rats compared to approximately 6-8 hours for the parent compound [13]. This enhanced persistence allows for prolonged tissue exposure and accumulation upon repeated exposure.

The tissue distribution of fipronil sulfone following exposure is extensive, with detectable residues in liver, kidney, brain, adipose tissue, reproductive organs, and even in milk and eggs of exposed animals [14]. The lipophilic nature of the

compound facilitates accumulation in lipid-rich tissues including the brain and endocrine organs, while the liver and kidneys serve as primary sites of metabolism and excretion, making them particularly susceptible to toxic insult. Despite this widespread tissue distribution and the documented in vitro toxicity of fipronil sulfone, comprehensive in vivo histopathological studies examining the structural consequences of exposure have been conspicuously absent from the scientific literature.

The reproductive system represents a potential target for fipronil sulfone toxicity, given the high lipid content and metabolic activity of testicular tissue. Spermatogenesis is a highly regulated process requiring precise hormonal control and intact cellular architecture [15]. Disruption of Leydig cell function, Sertoli cell integrity, or the seminiferous epithelial cycle can result in impaired fertility. Similarly, the seminal vesicles, as androgen-dependent accessory reproductive glands, may be vulnerable to endocrine-disrupting chemicals. Previous studies with other pesticides have demonstrated that xenobiotic exposure can induce metaplastic changes, alter secretory function, and compromise reproductive potential [16].

The kidney, as a primary excretory organ, receives high blood flow and concentrates toxicants during urine formation, making it susceptible to nephrotoxic injury. The proximal convoluted tubule, with its high metabolic activity and specialized transport functions, is particularly vulnerable to chemical insult [17]. Glomerular structures may also be affected, leading to altered filtration dynamics and proteinuria. Hepatic toxicity is similarly expected given the liver's central role in xenobiotic metabolism. The cytochrome P450 enzymes that generate fipronil sulfone are concentrated in hepatocytes, potentially leading to localized generation of reactive intermediates and oxidative stress [18]. The zonal organization of the liver, with periportal and pericentral regions exhibiting different metabolic capabilities, may result in region-specific patterns of injury.

The brain, and particularly the hippocampus, represents a critical target for neurotoxicants due to its high metabolic demand, limited regenerative capacity, and dependence on precise neuronal connectivity for cognitive function [19]. The hippocampus plays essential roles in learning, memory formation, and spatial

navigation, and damage to hippocampal neurons can have lasting functional consequences. Given fipronil sulfone's enhanced GABA receptor affinity and documented neurotoxicity in vitro, investigation of hippocampal histopathology following in vivo exposure is warranted.

The widespread use of fipronil has resulted in significant environmental contamination and human exposure. The United States Geological Survey has detected fipronil and its metabolites in urban streams across the United States at concentrations exceeding aquatic life benchmarks [20]. In agricultural settings, fipronil residues have been detected in soil, water, and produce. Perhaps most alarmingly, the 2017 fipronil contamination incident in Europe, where millions of eggs were contaminated with fipronil and subsequently distributed across multiple countries, demonstrated the potential for widespread dietary exposure [21]. In this incident, fipronil sulfone was detected as a major residue in contaminated eggs, highlighting the relevance of this metabolite to human exposure scenarios.

Despite the documented formation, persistence, and in vitro toxicity of fipronil sulfone, a comprehensive evaluation of its histopathological effects in vivo has not been conducted. This knowledge gap impedes accurate risk assessment and may result in underestimation of the true health risks associated with fipronil use. The present study was therefore designed to address this gap by evaluating the histopathological consequences of acute fipronil sulfone exposure in multiple organ systems of male mice, employing both qualitative histological examination and quantitative histomorphometric analysis using ImageJ software. The organs selected for examination—testis, seminal vesicle, kidney, liver, and brain—represent key targets based on the compound's toxicokinetics, known mechanisms of action, and potential functional consequences of structural damage.

This study provides the first comprehensive histopathological characterization of fipronil sulfone toxicity in vivo, establishing a foundation for future mechanistic investigations and informing risk assessment of this important pesticide metabolite. The findings have implications for regulatory decisions regarding acceptable exposure levels and for understanding the potential health consequences of fipronil contamination in food and the environment.

2. MATERIALS AND METHODS

2.1 Animals and Experimental Design

Sixteen adult male albino mice (*Mus musculus*), weighing 31.5-39 g, were procured from the National Institute of Health, Islamabad. Animals were housed in steel cages under controlled conditions (25±3°C, 40-60% humidity, 12:12 h light:dark cycle) with free access to standard rodent chow and tap water. After two-week acclimatization, mice were randomly divided into control and treated groups (n=8 per group). All procedures followed guidelines of The Ethical Committee, Faculty of Biological Sciences, Quaid-i-Azam University.

2.2 Dose Preparation and Administration

Fipronil sulfone (Sigma-Aldrich, USA) was dissolved in DMSO to prepare a stock solution (27 mg/2 ml). Based on calculated LD_{50} of 180 mg/kg, a sub-lethal dose of 100 mg/kg (55% of LD_{50}) was administered intraperitoneally to the treated group. Control animals received equivalent volumes of DMSO vehicle.

2.3 Tissue Collection and Processing

Twenty-four hours post-treatment, mice were anesthetized with ketamine hydrochloride and sacrificed. Liver, kidney, brain, testis, and seminal vesicles were excised, washed in PBS, and fixed in 10% paraformaldehyde. Tissues were dehydrated through graded alcohols, cleared in xylene, embedded in paraffin wax, and sectioned at 5 µm thickness using a microtome (Shandon Finesse, UK).

2.4 Histological Staining

Sections were stained with:

Hematoxylin and Eosin (H&E)** for general morphology

Periodic Acid-Schiff (PAS)** for glycogen and basement membranes

Trichrome** for connective tissue (Sigma-Aldrich kit)

Standard protocols were followed as previously described [11].

2.5 Histomorphometric Analysis

Images were captured using a light microscope (Leica, Germany) with digital camera (Cannon, Japan) at 10× and 40× magnifications. Morphometric measurements were performed using ImageJ-win64 software (NIH, USA). Parameters measured included:

Testis: Interstitial space, tunica albuginea thickness, seminiferous tubule diameter, epithelial height, tubular lumen diameter (50 measurements per group).

Seminal vesicle: Epithelial height (30 measurements per group).

Kidney: Renal corpuscle area, glomerular area, Bowman's space (30 glomeruli per group).

Liver: Number of degenerated hepatocytes around central veins (20 fields per group).

Brain: Number of degenerated hippocampal neurons (20 fields per group).

2.6 Statistical Analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical comparison between control and treated groups was performed using Student's t-test in Microsoft Excel. Differences were considered significant at $p<0.05$. Graphs were generated using GraphPad Prism.

RESULTS

3.1 Testicular Histopathology

Fipronil sulfone treatment induced significant alterations in testicular architecture (Figure 1, Table 1). Interstitial space increased by 65.1% (7.96±0.61 vs. 4.82±0.34 µm, $p<0.05$), indicating Leydig cell loss or dysfunction. Tunica albuginea thickness decreased by 33.4% (28.43±1.89 vs. 42.67±2.31 µm, $p<0.05$), compromising testicular integrity.

Seminiferous tubules showed marked degeneration with 20.8% reduction in diameter (168.32±7.54 vs. 212.45±8.67 µm, $p<0.05$) and 25.1% decrease in epithelial height (58.67±2.93 vs. 78.34±3.21 µm, $p<0.05$), indicating impaired spermatogenesis.

Tubular lumen diameter increased by 60.4% (72.56±3.78 vs. 45.23±2.45 μm, $p<0.05$), reflecting germ cell depletion.

Histological examination (Figure 1) revealed disrupted spermatogenesis, degenerated seminiferous tubules, and thinned tunica albuginea in treated animals compared to controls with normal architecture and complete spermatogenesis.

3.2 Seminal Vesicle Pathology

Seminal vesicle epithelial height increased significantly by 52.1% in treated animals (27.89±1.67 vs. 18.34±1.23 μm, $p<0.05$). Histologically, treated tissues showed marked metaplasia with transformation from columnar to cuboidal epithelium, reduced epithelial folding, and dilated lumens (Figure 2), indicating altered secretory function.

3.3 Renal Histopathology

Fipronil sulfone induced significant nephrotoxicity (Table 2, Figure 3). Renal corpuscle area decreased by 24.7% (3187±142 vs. 4234±156 μm², $p<0.05$) and glomerular area by 30.5% (1978±87 vs. 2845±98 μm², $p<0.05$). Bowman's space expanded by 81.7% (567±31 vs. 312±24 μm², $p<0.05$), indicating glomerular shrinkage. Proximal convoluted tubules showed degeneration, loss of brush border integrity, and increased luminal spaces. Medullary tubules exhibited disintegration and damage. Focal hemorrhages were observed in treated kidneys.

3.4 Hepatic Histopathology

The number of degenerated hepatocytes around central veins increased 3.7-fold in treated animals (12.7±1.3 vs. 3.4±0.5 per field, $p<0.05$). Histological examination revealed cytoplasmic vacuolation, glycogen accumulation, nuclear pyknosis, karyorrhexis, and pericentral necrosis (Figure 4). Increased Kupffer cells indicated inflammatory response. Central veins appeared enlarged with blood congestion.

3.5 Hippocampal Neurotoxicity

Hippocampal neurodegeneration increased 4.2-fold following fipronil sulfone exposure (21.6±2.1 vs. 5.2±0.8 degenerated neurons per field, $p<0.05$). Histological examination (Figure 5) revealed degeneration of dentate gyrus granular cells,

vacuolation, necrosis, pyknotic nuclei, and disorganization of pyramidal cell layers in cornus ammonis regions. Extracellular edema was evident.

4. DISCUSSION

This study provides the first comprehensive evidence that acute fipronil sulfone exposure induces significant multi-organ histopathological damage in mice. The findings demonstrate that this major fipronil metabolite, at a sub-lethal dose (55% of LD_{50}), causes structural alterations in reproductive, excretory, and neural tissues, with potential functional consequences. The testicular damage observed—reduced tubular diameter, epithelial height, and increased lumen size—indicates impaired spermatogenesis. Similar histopathological patterns have been reported with other pesticides [12,13], but this is the first documentation for fipronil sulfone. The increased interstitial space likely reflects Leydig cell loss or dysfunction, potentially compromising testosterone production [14]. The thinning of tunica albuginea may reduce testicular protection and structural integrity.

Seminal vesicle alterations—metaplasia, reduced folding, and increased epithelial height—suggest disrupted secretory function. Since seminal vesicle epithelium is androgen-dependent [15], these changes may reflect endocrine disruption. Fipronil sulfone's mitochondrial toxicity [16] could interfere with energy-dependent secretory processes, affecting seminal fluid composition.

The nephrotoxicity observed—reduced glomerular area, expanded Bowman's space, and tubular degeneration—indicates both glomerular and tubular damage. Glomerular shrinkage likely results from podocyte injury, as these cells are particularly vulnerable to oxidative stress [17]. Loss of brush border in proximal tubules would severely impair reabsorption of glucose, amino acids, and electrolytes. Similar patterns have been reported with other nephrotoxicants [18]. Hepatic damage, particularly pericentral necrosis, reflects the high metabolic activity of zone 3 hepatocytes and their sensitivity to toxic insults [19]. The increased Kupffer cell numbers indicate activation of hepatic macrophages in response to injury. Glycogen accumulation suggests metabolic disruption, possibly through interference with glycogenolysis or gluconeogenesis. Hippocampal neurodegeneration is particularly

concerning given the hippocampus's role in learning and memory [20]. The observed degeneration of dentate gyrus granular cells and pyramidal neurons could impair cognitive function. The mechanism likely involves both GABA receptor antagonism and oxidative stress, as previously demonstrated in vitro [8].

The greater toxicity of fipronil sulfone compared to fipronil may be explained by several factors. First, its higher affinity for mammalian GABA receptors [5] potentiates neurotoxicity. Second, its longer half-life [7] allows prolonged tissue exposure. Third, its lipophilicity facilitates accumulation in lipid-rich tissues like brain and reproductive organs. Fourth, its ability to induce oxidative stress [8] causes widespread cellular damage. These findings have important implications for risk assessment. Current regulations focus primarily on parent compounds, but metabolites may pose greater risks [1]. The detection of fipronil residues in food products [10] and the formation of sulfone metabolite in vivo suggest that human exposure occurs. The multi-organ damage observed at a sub-lethal dose in mice raises concerns about chronic low-level exposure in humans. Several study limitations should be acknowledged. The acute exposure model does not reflect typical environmental exposure patterns. The intraperitoneal route differs from oral or dermal exposure routes relevant to humans. Functional assessments (fertility, cognitive tests) were not performed to correlate with structural changes. Future studies should address these limitations and investigate molecular mechanisms.

5. CONCLUSION

This first comprehensive histopathological investigation demonstrates that acute fipronil sulfone exposure induces significant damage to testis, seminal vesicle, kidney, liver, and hippocampus in male mice. The quantitative histomorphometric analysis provides objective evidence of structural alterations that could compromise organ function. These findings highlight the importance of considering pesticide metabolites in toxicological evaluations and risk assessments. Further research is warranted to elucidate molecular mechanisms, assess chronic exposure effects, and evaluate potential protective interventions.

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