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FIPRONIL EXPOSURE: A GROWING CONCERN FOR REPRODUCTIVE HEALTH

Payal Malame[1], Dr. Mangala Thakare[2], Dr. Varsha Dhurvey[3], Nayan Kumbhare[4]

1. **Ms. Payal Malame,** Student, PGTD of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (M.S) India
2. ***Dr. Mangala Thakare***, Assistant Professor, PGTD of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (M.S) India.
3. ***Dr. Varsha Dhurvey***, Professor, PGTD of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (M.S) India..
4. ***Mr. Nayan Kumbhare,*** *Research Scholar*, PGTD of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (M.S) India.

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ABSTRACT:

Fipronil, a widely used insecticide, has been linked to reproductive toxicity in various species. This review summarizes the existing evidence on the effects of fipronil on the reproductive system, highlighting its impact on fertility, sperm quality, and gonadal development. Studies in mammals, birds, and insects consistently show that fipronil exposure leads to reduced fertility, decreased sperm count and viability, and altered gonadal morphology. The mechanisms underlying these effects involve disruption of hormonal balance, oxidative stress, and DNA damage. These findings have significant implications for human health, wildlife conservation, and environmental sustainability, emphasizing the need for stricter regulations and safer alternatives to fipronil.

***KEYWORDS*:** Fipronil, Reproductive toxicity, Fertility, Hormonal disruption, Histology.

INTRODUCTION:

Fipronil a phenyl pyrazole insecticide, was first developed by Rhône Poulenc Ag Company (now Bayer Crop Science) in 1987, it was introduced to the market in 1993 and registered for use in the United States in 1996[1,2,3]. Fipronil is (5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-fluoromethylsulfinyl pyrazole) a broad-spectrum insecticide belonging to

CORRESPONDING AUTHOR:	RESEARCH ARTICLE
Dr. Mangala Thakare Assistant Professor, PGTD of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (M.S) India Email: mangu81084@gmail.com	
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the phenylpyrazole chemical family, classified by the World Health Organization (WHO) as a Class II moderately hazardous pestiside, a potent phenylpyrazole insecticide[4].

Fipronil, a relatively new yet extensively utilized insecticide, has gained recognition for effectively addressing insect resistance and public health concerns typically associated with traditional pesticide families[5]. Fipronil based products, marketed under various trade names (Chipco VR, Choice, ICON 6.2FST, Over n' Out and TeckPac) have gained global popularity for effective

Fipronil has been detected in various environmental samples, its presence has been confirmed in surface water, urban waterways, rural rivers, and agricultural runoff, as well as in indoor and outdoor dust, soil, and wastewater effluent[7,8,9,10.] . Fipronil is susceptible to degradation in water and soil through various abiotic and biotic processes, resulting in the formation of several breakdown products, including: Fipronil sulfide (through reduction), Fipronil amide (through hydrolysis), Desulfinyl fipronil (through photolysis), Fipronil sulfone (through oxidation), these degradation products are formed when fipronil is present in soil or water, highlighting the importance of environmental factors in its breakdown[11,12]. Fipronil's sulfone metabolite and fipronil-desulfinyl, a photodegradation product, demonstrate enhanced toxicity to insect and non-target species compared to the parent compound[13]. In animals, fipronil undergoes primary metabolism to fipronil-sulfone via cytochrome P450-mediated oxidation [14].

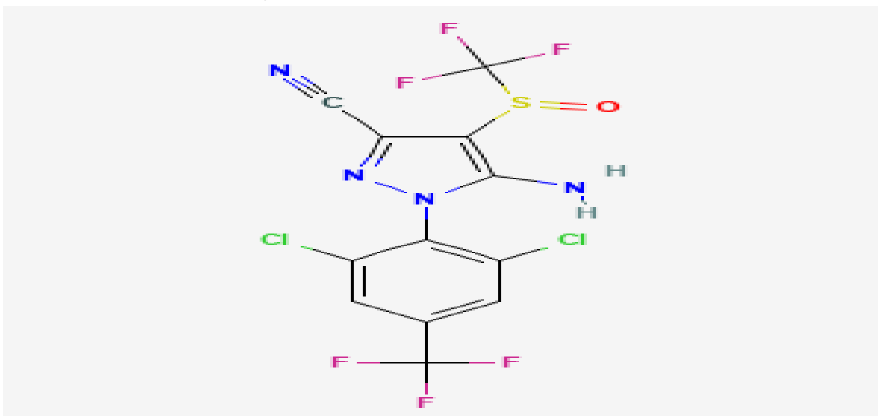

Fig: Chemical structure of Fipronil (https://pubchem.ncbi.nlm.nih.gov)

Fipronil is a white, powdery substance with a distinctive moldy smell[15]. Fipronil has the molecular formula $C_{12}H_4Cl_2F_6N_4OS$ and molecular weight of 437.1 g/mol. Its IUPAC name is 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(trifluoromethylsulfinyl)pyrazole-3-carbonitrile ,It is slightly soluble in water and has a melting point of 200-201°C. The density of fipronil is 1.477-1.626 g/cm3 at 20 °C. Fipronil has a low vapor pressure (2.78X10-9 mm Hg at 25 °C) and a high log Kow (4.0), which means that it is more likely to partition into organic matter than into water[16]. Fipronil insecticides are the only toxicants deliberately introduced into ecosystems as a targeted approach to improve food safety by effectively managing pest populations and regulating disease-transmitting vectors[17]. It controls pests like cockroaches, mosquitoes, locusts, fleas, lice and ticks in dogs, cats, and cattle[18,19].

General toxixcity

Studies in mice and rats have demonstrated that oral administration of fipronil leads to toxicological effects, including neurotoxicity, hepatotoxicity, reproductive toxicity, and disruption of endocrine function[20,21,22]. Fipronil's lipophilic characteristics facilitate its sequestration in highly lipidic tissues, such as the brain, resulting in extended persistence[23]. Human ingestion of fipronil can cause symptoms such as sweating, nausea, vomiting, headache, abdominal pain, dizziness, agitation, weakness, and seizures. Fortunately, these effects are typically reversible and resolve on their own[24]. Fipronil's use on rabbits has been discouraged by veterinarians due to adverse effects, including depression and decreased appetite [25].

Mode of action

Fipronil (FPN) functions as a GABAergic insecticide by binding to GABA receptors, inhibiting chloride ion uptake, and inducing uncontrolled hyperexcitation, convulsions, and cellular mortality in invertebrates[26]. Research indicates that fipronil completely inhibits various human glycine receptor subtypes (α1, α1β, α2, and α3), mirroring its potency at vertebrate GABAA receptors, implying potential toxicity across all glycine receptor isoforms[27,28].

Mode of action on sperm[29].

Fipronone enters spermatozoa

↓

Binds to GABA receptors (GABAARs)

↓

Blocks GABA's action

↓

Inhibits influx of essential ions (HCO3− and Cl−)

↓

Disrupts GABA system activation

↓

Interferes with GABAergic signaling and intracellular interactions

↓

Compromises sperm capacitation

↓

Impairs fertilization

METHODOLOGY

Literature searches were conducted using PubMed, Google Scholar, Science Direct, and Scopus. Data was extracted from abstracts and introductions of included studies, focusing on study design and duration, fipronil exposure levels and duration and models for research.

This review synthesizes two decades of research (2004-2024) on fipronil's effects on male and female reproductive systems.

EFFECT OF FIPRONIL ON REPRODUCTIVE SYSTEM

Hematological evaluation

Several studies have reported decreases in RBC-related parameters following fipronil exposure, significantly decreases in RBC count, hemoglobin, and hematocrit in treated animals, though the specific dose of 0.3 mg/1 mL was associated with increased WBC counts in monkeys[30]. Decreased packed cell volume, hemoglobin, total erythrocyte count, and total leucocyte count in White Leghorn cockerels exposed to fipronil at doses of 1, 5, and 10 mg/kg was reported[31]. Similar reductions in erythrocyte count and hemoglobin content in Nile Tilapia was observerd at concentrations of 0.014, 0.0042, and 0.002 mg of fipronil[32] and erythrocyte counts, hemoglobin, and hematocrit decreased in Cyprinus carpio exposed to fipronil at 0.08 mg/L and 0.10 mg/L[33]. Significant reductions is seen in erythrocyte indices (MCV, MCH), hemoglobin, RBCs, hematocrit, lymphocytes, and platelets[34]. Decreased of hematocrit level in Rhamdia quelen at 0.3 and 0.4 mg/L, further highlighting the impact on RBC-related parameters[35] .

Sr.no	Model	Doses	Duration	Interference	Reference
1.	Adult Rhesus Monkeys	0.3 mg/1 mL	4 hour	Exhibited significant decreases in red blood cell (RBC) count, hemoglobin, and hematocrit. Conversely, white blood cell (WBC) counts were elevated	Khan *et al*., (2003)
2.	White Leghorn cockerels	1, 5, and 10 mg/kg	100 days	Fipronil's resulted in significant decreases in packed cell volume, hemoglobin levels, total erythrocyte count, and total leucocyte count	Adhikari *et al*., (2014)
3.	Nile Tilapia	0.014, 0.0042, and 0.002 mg of fipronil	10 weeks	Fipronil resulted in significant decreases in erythrocyte count, hemoglobin content, and total leukocytic coun	El-Murr *et al*., 2015
4.	Cyprinus carpio	Fipronil exposure 0.08 mg/L and 0.10 mg/L	12 days	Significantly decreased erythrocyte count, hemoglobin, and hematocrit, conversely, mean corpuscular volume, total leukocyte count, neutrophils, monocytes, and lymphocytes were	Ghaffar *et al*., (2018)

				significantly increased in Cyprinus carpio	
5.	Male albino mice	Fipronil (1.44 mg/kg b.w)	28 days	Reductions in erythrocyte indices (MCV, MCH), hemoglobin, RBCs, hematocrit, lymphocytes, and platelets	Abouelghar *et al*.,(2019)
6.	36 silver catfish	f 0, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.8 mg L–1 of fipronil.	96 Hours	Including decreased hematocrit rates at 0.3 and 0.4 mg L^{-1}, and decreased white blood cell and total thrombocyte counts	Fredianelli *et al.*, (2019).

Weight response

Studies have consistently demonstrated that fipronil intoxication leads to a decrease in testicular weight. Fipronil caused a significant decrease in the relative weight of testes in rats at a dose of 4.5 mg/kg at day 20 of exposure[36]. A significant reduction in testicular size in males and a marked decrease in ovarian size in females after treatment with 0.05% fipronil[37]. In subsequent studies, a dramatic decrease in the weight of the testes index, epididymis, and accessory sex organs following fipronil administration[38] and reductions in both body weight and organ weight of testis after oral administration of fipronil at 24.25 mg/kg[39]. Most recently, a significant reduction in the testis weight/body weight ratio was observed[40], further supporting the findings of previous studies.

Sr.no	Model	Doses	Duration	Interference	Reference
1.	60 adult male cockerels	. Fipronil(1.5 ,2.5 , 3.5 and 4.5	60 day	Decrease in the relative weight of testes in rats	Hussian *et al*.,(2018)
2.	Blaps polycresta	0.05% fipronil	3 days	Induced morphological deformities in the external reproductive structures of males and a notable deformation in one ovary of females, reduction in testicular size.	Osman W., 2018
3.	36 Male albino rats	20 mg Fipronil /kg and	60days,	Fipronil exposure causes severe damage to reproductive organs, decrease in the weight of the testes index, epididymis, and accessory sex organs	Tohamy *et al*.,(2021)
4.	Albino rats	Fipronil (24.25 mg/kg b.wt)	90 days	Fipronil reduced body weight and organ weight Histopathological damage testis, Increased sperm morphological abnormalities	**Verma(2022).**

				and Decreased sperm motility, viability, and density	
5.	48 Male albino rats	Fipronil(1/30 and 1/60 LD50)	3 months	Fipronil exposure leads to testicular atrophy, mild diffuse degeneration was observed in the seminiferous tubules, accompanied by epithelial thinning and sertoli cells vacuolation, there were significant reduction in sperm count, reduction in the testis weight.	Abdel-Mobdy *et al.,(*2024)

Sperm motility and morphology

Numerous studies have highlighted significant alterations in sperm morphology, motility, and viability after exposure to fipronil. For example, substantial decreases was observedin sperm density, motility, viability, and normal morphology, as well as an increase in sperm abnormalities[41] ,a concentration of 0.1 µg/L of fipronil decreased spermatozoa concentration and sperm viability, while increasing sperm metabolic rate[42] as well as impaired sperm motility was observed, with a notable reduction in progressive motile spermatozoa and an increase in non-motile spermatozoa after exposure to 3 mg/kg fipronil[43]. Subsequent studies, confirmed the negative impact of fipronil on fertility, demonstrating a decrease in spermatozoa quantity and increased spermatozoa mortality[44]. Exposure to a 0.05% fipronil solution induced morphological deformities in the external reproductive structures of males and caused notable deformation in the ovary of females[37].Further evidence of fipronil's genotoxicity by reporting structural chromosome aberrations and sperm abnormalities induced by fipronil exposure[34]. More recent studies have continued to demonstrate the adverse effects of fipronil on sperm quality,high concentrations of fipronil significantly impaired various sperm motility parameters[29]. Substantial decreases was observed in sperm density, motility, viability, and normal morphology after exposure to concentrations ranging from 5-20 mg/kg of fipronil[38].Fipronil exposure negatively affected sperm quality, leading to increased sperm morphological abnormalities and decreases in sperm motility, viability, and density[39]. Impaired sperm motility after exposure to 10-200 µM fipronil[45] further confirmed these findings, demonstrating that fipronil exposure significantly impaired sperm motility and kinematics[46].

Sr.no	Model	Doses	Duration	Interference	Reference
1.	32 Male rats	Fipronil (2.5,5.0 and 10mg/kg)	4 week	Fipronil exposure causes significant damage to sperm, including reduced viability, motility, and acrosome integrity. This damage is likely due to increased oxidative stress and	Khan *et al.,(*2015)

				lipid peroxidation, leading to sperm apoptosis.	
2.	Honey bees (drones)	0.1 µg/L of fipronil	20 days	Decrease spermatozoa concentration and sperm viability, while increasing sperm metabolic rate, ultimately impairing drone fertility	Kairo *et al.*, 2016
3.	Male rats	(0.03, 0.3 or 3 mg kg^{-1})	Gestational Day 15 until Postnatal Day 7.	It alters sperm motility, reducing motile spermatozoa and increasing non-mobile spermatozoa, potentially compromising sperm quality.	Barros *et al .,(2016)*
4.	Honey bees(drones)	0.1 µg - L^1fipronil1	20 days	Fipronil did not impact drone survival, maturity, or semen volume, it did negatively affect fertility. This was due to a reduction in spermatozoa quantity coupled with increased spermatozoa mortality	Kairo *et al.*, 2017
5.	Blaps polycresta	0.05% fipronil	3 days	Induced morphological deformities in the external reproductive structures of males and a notable deformation in one ovary of females	Osman W. 2018
6.	Male albino mice	Fipronil (1.44 mg/kg b.w)	28 days	Fipronil to induce genotoxic effects involving structural chromosome aberrations (SCAs) and sperm-shape abnormalities. The mechanism of this genotoxic effects could be also attributed to reactive oxygen species (ROS)-mediated oxidative stress .	Abouelghar *et al.*,(2019)
1.	Male mouse	(0.1, 1, 10, 100, and 300 µM)	Incubated at 37 °C for 2 h	FPN treatment significantly reduced sperm motility, motion kinematic parameters, and intracellular ATP level, whereas the acrosome reaction was enhanced	Bae *et al.*,2020
2.	36 Male albino rats	20 mg Fipronil /kg and	60days,	Fipronil exposure causes severe damage to reproductive organs, leading to decreased sperm quality, reduced testosterone levels, and impaired fertility	Tohamy *et al.*,(2021)
3.	Albino rats	Fipronil (24.25 mg/kg b.wt)	90 days	Fipronil reduced body weight and organ weight Histopathological damage testis, Increased sperm morphological abnormalities and Decreased sperm motility, viability, and density	**Verma(2022).**
4.	Boar spermatozoa	Fipronil(10-200 µM)	30 minutes and 2 hours of incubation	Sperm motility in all fipronil treatment groups at 30 min, 2 hrs of incubation, gradual reduction in motion kinematics significantly	Adikari *et al.*, (2022)

				higher percentage of dead sperm was observed at 200 µM fipronil	
5.	Male rat spermatozoa	fipronil exposure(0.1,1 ,10,100 and 300 µM	90 minutes. Two-dimensional electrophoresis	Reduced sperm motility and ,fipronil exposure led to decline in capacitated sperm drastic increase in the number of acrosome reacted sperm and deficiencies in intracellular ATP level	Bae *et al.*,(2024)

Immunohischemistry

In recent studies, the effects of fipronil exposure on reproductive health have been extensively investigated. Fipronil exposure induced apoptosis in spermatogenic and epididymal cells, evidenced by a strong Casp3 reaction, Furthermore, they observed reduced cell proliferation in the testis and epididymis, as indicated by a weak PCNA reaction[47],further impact of fipronil, reveal the absence of immunostaining for spermatogonia and spermatocyte nuclei in most seminiferous tubules at administration of 20 mg/kg, suggesting a disruption in sperm cell development and maturation, which could impair fertility[38]. More recently apoptotic changes in the reproductive organs of rats occurred , with increased BAX marker expression in the liver and testis following fipronil exposure (10 mg/kg for 6 weeks), indicating enhanced apoptotic activity[48]. Together, these studies highlight the potential detrimental effects of fipronil on reproductive health, specifically by inducing apoptosis and disrupting normal cellular processes in the testis and epididymis.

Sr.no	Model	Doses	Duration	Interference	Reference
1.	28 Male mature rats	fipronil (5 mg/kg)	28 days	Fipronil exposure induced apoptosis in spermatogenic and epididymal cells, evidenced by a strong Casp3 reaction, Furthermore, they observed reduced cell proliferation in the testis and epididymis, as indicated by a weak PCNA reaction	Saleh *et al.*,(2020)
2.	36 Male albino rats	20 mg Fipronil /kg and	60days,	Fipronil exposure causes severe damage to reproductive organs, leading to decreased sperm quality, reduced testosterone levels, and impaired fertility	Tohamy *et al.*,(2021)
3.	24 Male wistar rats	10mg/kg fipronil	6 weeks	Reduce sperm count in epididymis and increase abnormal sperm in testis, Testicular damage evident with thickened tunica albuginea, interstitial edema, irregular seminiferous tubules ,widened lumen,separation of germinal cell layers and reduced sperm and leydig cells, epdidymal lesions and BAX marker increased.	Nakul (2024)

Histological alteration

Male

Several studies have documented the detrimental effects of fipronil on male reproductive systems, The highest radioactivity levels of fipronil sulfone were detected in testes following oral administration of fipronil (10-1 mg/kg)49. More severe damage, including necrosis, epithelial desquamation, and germ cell depletion, following subacute exposure to 10 mg/kg fipronil for 28 days50. At 5-10 mg/kg fipronil induced severe degenerative and necrotic changes in rat seminiferous tubules, leading to spermatogonia depletion and spermatozoa loss41. Testicular damage in cockerels at 3.5 mg/kg and 4.5 mg/kg, with thinner and disorganized seminiferous tubule epithelium, abnormal spermatozoa, and degenerative/necrotic cells at days 20, 40, and 6036. Severe testicular lesions, cystic dilatation of seminiferous tubules, arrested spermatogenesis, smooth muscle hypertrophy, and spermatogonial cell vacuolation in Coturnix japonica administered fipronil at LD50 values of 2.26 mg/kg and 11.3 mg/kg51. Even lower doses (5 mg/kg) of fipronil have been linked to reproductive toxicity in rats, including edema, spermatogenesis degeneration, and reduced sperm count47. Significant histopathological changes in mice testes exposed to 100 mg/kg fipronil sulfone52. 20 mg/kg fipronil for 60 days caused testicular and epididymal damage, characterized by exfoliation, necrosis, degenerative changes, shedding, vacuolation, and inflammation38,Chronic exposure to 1/30 and 1/60 of the LD50 of fipronil resulted in mild widespread degeneration of seminiferous tubules, decreased lining epithelium thickness, and Sertoli cell vacuolation40. A range of alterations, including thickened tunica albuginea, interstitial edema, variations in seminiferous tubule size, reduced Leydig cell numbers, and disrupted germinal cell layers after exposure to 10 mg/kg fipronil for 6 weeks 48.

Sr.no	**Model**	**Doses**	**Duration**	**Interference**	**Reference**
1.	Male rats	Fipronil oral dose (10 mg/kg)		Tissue analysis revealed highest radioactivity levels in adipose tissue, adrenals, liver, kidney, testes, primarily attributed to fipronil-sulfone.	Cravedi *et al.*,(2013)
2.	24 Female swiss albino mice	10 mg/kg fipronil	28 days	Fipronil causes severe damage to the testes, leading to necrosis, epithelial desquamation, and reduced fertility	Badgujar *et al.*,(2014)
3.	32 Male rats	fipronil (2.5,5.0 and 10mg/kg)	4 week	Fipronil exposure causes severe degenerative and necrotic changes in rat seminiferous tubules, leading to spermatogonia depletion and spermatozoa loss	Khan *et al.*,(2015)
4.	60 adult male cockerels	. Fipronil(1.5 ,2.5 , 3.5 and 4.5	60 day	Thinner and disorganized seminiferous tubule epithelium, abnormal spermatozoa, and degenerative/necrotic cells	Hussian *et al.*,(2017)
5.	Male Coturnix japonica	2.26 mg/kg and 11.3 mg/kg,	15 days	Observed severe testicular lesions, cystic dilatation of	Khalil *et al.*, (2017)

				seminiferous tubules, arrested spermatogenesis, smooth muscle hypertrophy, and spermatogonial cell vacuolation	
6.	28 Male mature rats	fipronil (5 mg/kg)	28 days	Fipronil causes severe damage to the testes, including fluid accumulation, edema, spermatogenesis degeneration	Saleh *et al.*,(2020)
7.	Sixteen Male mice	fipronil sulfone(100 mg/kg)	2 weeks	Fipronil sulfone causes severe damage to the testes, including changes in testicular morphology, damaged sperm production, and potential infertility	Suliman (2020)
8.	36 Male albino rats	20 mg Fipronil /kg and	60days,	Fipronil exposure causes testicular and epididymal damage, characterized by exfoliation, necrosis, degenerative changes, shedding, vacuolation, and inflammation.	Tohamy *et al.*,(2021)
9.	48 Male albino rats	Fipronil(1/30 and 1/60 LD50)	3 months	Fipronil exposure leads to testicular atrophy, mild diffuse degeneration was observed in the seminiferous tubules, accompanied by epithelial thinning and sertoli cells vacuolation, there were significant reduction in sperm count.	Abdel-Mobdy *et al.*,(2024)
10.	24 Male wistar rats	10mg/kg fipronil	6 weeks	Reduce sperm count in epididymis and increase abnormal sperm in testis, Testicular damage evident with thickened tunica albuginea, interstitial edema, irregular seminiferous tubules ,widened lumen,separation of germinal cell layers and reduced sperm and leydig cells, epdidymal lesions, reduced sperm density and loss of stereocilia and BAX marker increased.	Nakul (2024)

Female

Fipronil's impact on female reproduction is a growing concern. Early studies on ticks reported significant alterations in oocyte development. Dose-dependent histological alterations in Rhipicephalus sanguineus oocytes, including mild alterations at 1 ppm, extensive vacuolation and ruptured yolk granules at 5 ppm, and severely altered oocytes with extensive vacuolation and loss of normal morphology at 10 ppm. The following year, fipronil caused significant alterations in Rhipicephalus sanguineus oocyte development, including cytoplasmic vacuolation, reduced microvilli, and altered germ vesicle shape[54]. No abnormalities or treatment-related effects in the ovaries and thyroid of female rats exposed to fipronil at 0.1, 1.0, or 10.0 mg/kg/day[55]. More recent studies have continued to investigate fipronil's effects on female reproduction. Peripheral vacuolations in all oocytes of engorged Rhipicephalus microplus ticks exposed to fipronil[56]. Ovarian damage in Rhipicephalum microplus ticks treated with a combination of fentanyl and fluazuron, including cytoplasmic disorganization, degradation, vacuolization, and altered oocyte developmental stage distribution[57].

Sr.no	Model	Doses	Duration	Interference	Reference
1.	Rhipicephalus sanguineus tick oocytes	1 ppm,5ppm, 10ppm fipronil	Immersed in Petri dishes containing the above different concentrations of fipronil, for 2 min	fipronil exposure caused dose-dependent histological alterations in oocytes, at 1 ppm, mild alterations were observed, while 5 ppm caused extensive vacuolation and ruptured yolk granules. The highest concentration of 10 ppm resulted in severely altered oocytes with extensive vacuolation and loss of normal morphology	Oliveira *et al*., 2008
2.	60 partially fed females of *R. sanguineus*	fipronil (1, 5 and 10 ppm)	Immersed in fipronil for 2 minutes and incubated for 7 days	Causes structural damage to even fully developed oocytes. extensive cellular damage, including - Disrupted plasmic membrane mitochondrial damage ,altered protein synthesis (affected protein granules),disrupted plasmic membrane,Mitochondrial damage, altered protein synthesis.	Oliveira *et al*.,(2009)
3.	40 female rats	fipronil(0.1, 1.0, or 10.0 mg/kg/day)	6th to the 20th day	No treatment-related effects on ovaries and thyroid glands, no pathological abnormalities observed,	Magalhaes *et al*.,(2015)
4.	Rhipicephalus microplus (Acari: ixodidae female			Oocytes displayed peripheral vacuolations. Ultra-thin sections of the synganglion revealed distinct damage patterns, fipronil caused severe rupture of neural lamella and perineurium leading to neural cell apoptosis, whereas amitraz induced destruction of the neuropile region and widespread vacuolation in type I and II cortical cells.	Fular *et al*.,(2022)
5.	Rhipicephalus microplus females	Fipronil((1.25 mg/kg)	20 days	The ovaries of females morphological changes, including: cytoplasmic disorganization, cytoplasmic degradation, irregular shape of the oocyte and germinal vesicle, reduction and vacuolization of yolk granules and oocyte disruption, ocytes were observed in smaller numbers In determinate oocytes were verified in the ovaries of the treated groups	Secchis *et al*.,(2022)

Hormone analysis

Fipronil 70 mg/kg altered hormone levels, increasing plasma progesterone and decreasing estradiol 96 hours post-treatment, suggesting endocrine-disrupting effects[20]. Later decreased testosterone levels in rats exposed to high doses of fipronil. In addition to these hormonal disruptions, research on fipronil's interaction with estrogen signaling pathways revealed that fipronil and its sulfone metabolite acted as estrogen receptor alpha (ERα) inhibitors, demonstrating anti-estrogenic activity[59]. Further studies, demonstrated that fipronil (0.03, 0.3, or 3 mg/kg) led to long-term effects on the epididymis, reducing testosterone secretion and suggesting interference with the hypothalamic-pituitary-gonadal axis[43],and 25 µM fipronil selectively downregulated ERα expression and its regulated gene CDC2, as well as the upstream signaling molecule PES1, indicating disruption of ERα-mediated signaling[60]. Moreover decreased testosterone and increased estradiol (E2) levels in Coturnix japonica at fipronil LD50 values of 2.26 mg/kg and 11.3 mg/kg, reported respectively[51]. Similarly, it was found that 3.23 mg/kg fipronil significantly reduced estradiol levels in male rats[61]. Moreover, exploration of the enantiomer-specific disruptions in hormonal activity of fipronil, emphasizing the importance of evaluating the endocrine-disrupting potential of phenylpyrazole insecticides on an enantiomer-specific basis[62]. Further it was found that fipronil treatment led to a marked decrease in both testosterone and luteinizing hormone (LH) levels[63], a finding corroborated where reduced testosterone levels were found by exposure of fipronil[48].

Sr.no	**Model**	**Doses**	**Duration**	**Interference**	**Reference**
1.	Female wistar rats	Fipronil(70, 140 and 280 mg/kg	96 h or 20 days	Fipronil treatment disrupted and extended estrous cycles, reduced pregnancy rates, and significantly altered Plasma progesterone and estradiol levels.	Ohi *et al.,(*2004)
2.	Male Long–Evans rats	High doses (25, 50 mg/kg)	14 days	Exposure to high doses of fipronil resulted in a significant decrease in testosterone levels of rats	Moser *et al.*, (2014),
3.	Chinese Hamster Ovary (CHO-K1) cells	fipronil (6.4×10^{-7}M fipronil sulfone 9.8×10^{-7} M	for 24 hrs	Fipronil and fipronil sulfone act as estrogen receptor antagonists (ERα) without agonistic activity	Lu *et al*.,(2015)
4.	Male rats	(0.03, 0.3 or 3 mg kg^{-1})	0	It alters sperm motility, reducing motile spermatozoa ,reducing testosterone secretion and suggesting interference with the hypothalamic-pituitary-gonadal axis	Barros *et al .,(2016)*
5.	Female wistat rat plasma	Fipronil(25 µM)	48 hours	Fipronil down-regulates ERα expression, reduces CDC2 gene expression,suppresses PES1	Okazaki *et al.,(*2016)

6.	Male Coturnix japonica	2.26 mg/kg and 11.3 mg/kg,	15 days	Significant alterations in hormone levels, with a decrease in testosterone and an increase in estradiol (E2) levels o	Khalil *et al.*, (2017)
7.	Male rats	exposure to fipronil (3.23 mg/kg	12 week	Significantly reduced (estradiol levels	Abdelrazek *et al*., (2017)
8.	Sixty Male New Zealand rabbits	(354 mg/kg fipronil) spirulina (10 g/kg of diet daily	4 weeks	Fipronil administration led to significantly decrease testosterone, LH, T3, and T4 levels as well as higher TSH level as recorded in fipronil	Howayda *et al.,* (2022)
9.	Female rats			Fipronil, ethiprole, and flufiprole display anti-estrogenic effects, as evidenced by a dual-luciferase reporter gene assay, which revealed enantiomer-specific disruptions in hormonal activity,	Hu *et al*.,(2022)
10.	24 Male wistar rats	10mg/kg fipronil	6 weeks	Reduce sperm count in epididymis and increase abnormal sperm in testis, Testicular damage evident with thickened tunica albuginea, interstitial edema, irregular seminiferous tubules ,widened lumen,separation of germinal cell layers and reduced sperm and leydig cells, epddidymal lesions, reduced sperm density and loss of stereocilia and BAX marker increased.	Nakul (2024)

Biochemical analysis

Exposure to a sexes pesticide mixture fipronil (97and 95 mg/kg)–imadacloprid 450 mg/kg in both sexes for 28 days resulted in significant alterations in serum biochemical parameters, including a significant increase in the activity of serum enzymes, such as aspartate aminotransferase , alanine aminotransferase , alkaline phosphatase , urea, and gamma-glutamyltransferase , additionally, the study recorded a significant decrease in the level of serum uric acid, while total protein, albumin, and globulin concentrations were higher in treated rats, these biochemical changes were accompanied by a significant decrease in testicular DNA and RNA concentrations in a dose-dependent manner, as well as decreased testicular glutathione (GSH) levels[64]and exposure to 100 µM fipronil (FPN) led to significant alterations in cell cycle regulation, including increased levels of inactivated CDK1, as well as elevated expression of P53 and P21 proteins in oocytes[65].

Sr.no	Model	Doses	Duration	Interference	Reference
1.	28 Adult male rats,	0.547,0.409,0.820 mg/bw/day) of imidacloprid and fipronil mixture	28 days,	The combination of fipronil and imidacloprid causes severe damage to testicular DNA and RNA, reduces antioxidant levels, and increases oxidative stress, leading to testicular genomic decline	Badawy *et al., (2018)*
2.	Porcine ovaries	Fipronil (0,30,50,100µM	44 hours	Fipronil exposure impaired oocyte maturation by Decreasing polar body extrusion, Arrested germinal vesicle stage, further Increased ROS levels and DNA damage, Enhanced apoptosis and mitochondrial dysfunction, Disrupted cell cycle progression (CDK1 cyclin B-1)and Activated ATM-P53-P21 pathway	Zhou *et al.,(*2019)

Effect of fipronil on Membrane lipid peroxidation

Fipronil (FIP) exposure significantly elevated lipid peroxidation in vivo, as evidenced by increased malondialdehyde (MDA) concentrations in spermatozoa of male Wistar rats treated with FIP at doses of 2.5, 5, and 10 mg/kg body weight for 28 days[41],similarly administration of fipronil at a dose of 5 mg/kg significantly elevated MDA levels in testis o rats[66].

Sr.no	Model	Doses	Duration	Interference	Reference
1.	32 Male rats	Fipronil (2.5,5.0 and 10mg/kg)	4 week	Fipronil exposure causes significant damage to sperm, including reduced viability, motility, and acrosome integrity. This damage is likely due to increased oxidative stress and lipid peroxidation, leading to sperm apoptosis.	Khan *et al.,(*2015)
2.	Male rats	Fipronil 5mg/kg and 5mg/kg fipronil + vitamine	14 days,	Fipronil causes a decrease in sperm concentration and testicular glutathione levels, leading to oxidative stress and sperm depletion, elevated	Mazzo *et al.*, (2018)

		E 100 mg/kg for		MDA levels in testis of rats.	

Reactive oxygen species

Treatment of Wistar rats with FIP at doses of 2.5, 5, and 10 mg/kg body weight revealed that higher doses (5 and 10 mg/kg) led to a significant elevation in sperm reactive oxygen species (ROS) production[41]. Exposure to 100 µM fipronil (FPN) was found to induce apoptosis and cell cycle arrest during porcine oocyte maturation, likely due to elevated reactive oxygen species (ROS) levels.

Sr.no	**Model**	**Doses**	**Duration**	**Interference**	**Reference**
1.	32 Male rats	Fipronil (2.5,5.0 and 10mg/kg)	4 week	Fipronil exposure causes significant damage to sperm, including reduced viability, motility, and acrosome integrity. This damage is likely due to increased oxidative stress and lipid peroxidation, leading to sperm apoptosis.	Khan *et al.,(*2015)
2.	Porcine ovaries	Fipronil (0,30,50,100µM	44 hours	Fipronil exposure impaired oocyte maturation by Decreasing polar body extrusion, Arrested germinal vesicle stage, further Increased ROS levels and DNA damage, Enhanced apoptosis and mitochondrial dysfunction, Disrupted cell cycle progression (CDK1 cyclin B-1)and Activated ATM-P53-P21 pathway	Zhou *et al.,(*2019) Apoptosis

Fipronil impact on embroys

Embryotoxicity in fish exposed to fipronil, with malformations such as uninflated swim bladders at 100 µg/L, reduced body length at ≥ 200 µg/L, and spinal curvature at 400 µg/L. A dose-dependent relationship was observed between fipronil exposure and both reduced body length and curved body deformities[67]. Investigated the effects of fipronil (0.1-910 µg L−1) on embryonic development in Japanese medaka (Oryzias latipes). Over a 14-day exposure period, they observed a positive dose-response relationship for reduced hatching success and increased gross deformities, particularly tail curvature. The lowest-observed-effect concentration was 200 µg L−1, while delayed hatching occurred at concentrations ≥ 600 µg L−1[68]. Fipronil exposure at 1/10 LD50 (2.1 mg/kg b.wt) significantly decreased placenta weight, fetal weight, and fetal length. Furthermore, they observed various malformations, including head, thorax, and abdomen malformations, as well as cleft palate[69]. Detrimental effects of fipronil on embryonic development in vitro at concentrations of 1 µM and above. Stereomicroscopic evaluation revealed a concentration-dependent decrease in blastomere numbers at 10 µM, and fluorescence staining showed a significant increase in cell death starting at 1 µM. Complete degeneration of all embryos in female rats was observed following exposure to 10 µM fipronil[70].

Sr.no	Model	Doses	Duration	Interference	Reference
1.	Zebrafish embryo	100 µg/L, 200 µg/L, 400 µg/L Fipronil	6 to 120 hpf	Significant embryotoxicity, inducing malformations such as uninflated swimbladders at 100 µg/L, reduced body length at ≥ 200 µg/L, and spinal curvature at 400 µg/L	Yan *et al.,* (2016)
2.	Japanese medaka (Oryzias latipes	fipronil concentrations ranging from 0.1-910 µg L−1 for	14 days	Significantly impacted embryonic development in with a positive dose-response observed in reduced hatching success and increased gross deformities, particularly tail curvatur	Wagner *et al.,* 2017
3.	Female pregnant rats	Fipronil's(2.1 mg/kg and 0.7 mg/kg b.wt)	6th to 15th days of pregnancy Statistical Analysis Weight analysis	Maternal weight gain decreased, Fetal body weight and length significantly decreased,Fetal abnormalities increased, Heart and lungs hypoplasia.	Eisa *et al.,(*2017)
4.	Female rats	Fipronil in vitro(100, 10 and 1 µM) and in vivo(0.009 and 0.9 mg/kg BW)	Starting on Day 1 and finishing on Day 3 of pregnancy In vivo experimental design In vitro experimental design	Fipronil hindered embryonic development,reduced blastomere numbers, Increased cell death, FIPRON spot-on caused massive embryo degeneration.	Šefčíková *et al.*,(2018)

CONCLUSION

Fipronil exposure has been consistently linked to reproductive toxicity, causing a range of adverse effects including testicular damage, reduced testosterone secretion, inhibition of estrogenic activity, and abnormal spermatozoa. These findings suggest that fipronil can have significant and long-lasting impacts on reproductive health, highlighting the need for careful consideration and management of its use to minimize potential har

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