REVIEW ARTICLE

Pyrethroid-Induced Reproductive Toxico-Pathology in Non-Target Species

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ABSTRACT

Pesticides used against agricultural pests and ecto-parasite infestation in animals may also induce injurious effects in humans, pets and farm animals. The pyrethroid pesticides are rapidly replacing other insecticides due to relatively lower toxicity for mammals. However, they have now become an environmental issue due to excessive use in agriculture, livestock production, leather industry and shampoos etc. In addition to various clinical, hemato-biochemical, immunosuppressive and neuro-toxicological effects of pyrethroids, more danger has been suspected with respect to reproductive toxicity. The fetal resorption and early fetal mortality rate were found to be significantly increased in female animals allowed mating with males exposed to pyrethroids. The testicular and epididymal sperm counts and serum testosterone concentrations in pyrethroid treated animals were decreased. Moreover, abnormal spermatozoa, degenerated spermatozoa, arrested spermatogenesis and connective tissue proliferation in testes, and tailless spermatozoa in epididymis were reported with pyrethroid exposure. A decrease in pregnancy rate, number of implantation sites and total number of recovered fetuses have also been reported in female animals receiving pyrethroid treatment during gestation and allowed mating with untreated male rabbits. The progeny of pyrethroid exposed parents also showed toxic effects. Disruption of certain steroidogenic enzymes and nuclear receptors in has been reported in pyrethroid exposed animals. This review concludes that pyrethroid exposure is responsible for endocrine disruption and decreases fertility in both sexes of various non-target species and produces fetal mortality, which may be prevented by vitamin E supplementation due to its anti-oxidant potential.

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INTRODUCTION

Pesticides (insecticides, herbicides and fungicides) constitute the major potential environmental hazard to humans and animals as these are present and concentrated in the food chain. About 25-77 million poisoning cases including one million severe unintended pesticide poisonings (Zhang *et al.*, 2011) and 0.22 million casualties (Yashmashito *et al.*, 1997) by insecticides annually have been reported. World Health Organization has prohibited the use of pesticides having acute toxicity, but pyrethroids use is extensive in Pakistan (Aslam *et al.*, 2010; Ahmad *et al.*, 2011). Different pyrethroids are extensively and widely used against ectoparasites in domestic animals. Although spraying the walls of poultry house or stud/livestock farm is considered sufficient,

however, application directly to the back of grazing animals is necessary (Ahmad, 2010). This practice leads to their residues in animal food commodities. The chemical structures and uses of a few pyrethroids have been presented in Table 1.
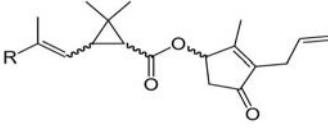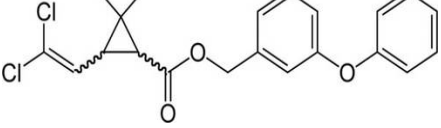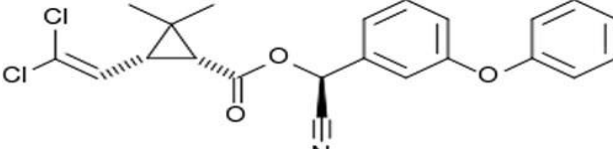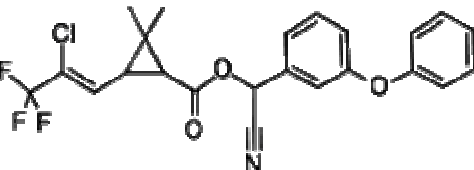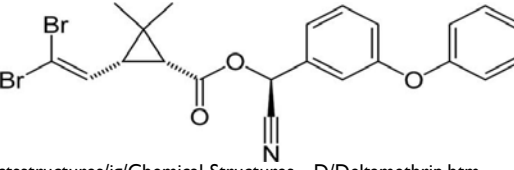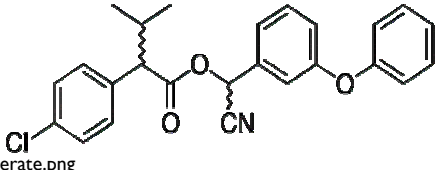
The pyrethroid insecticides are of three types: Type I (T syndrome) pyrethroids produce abnormal sensitivity and coarse tremors leading to prostration. Type II (CS syndrome) pyrethroids produce ptyalism and coarse tremors progressing to twisting movement of the neck and tail, while type I/II or TS pyrethroids produce signs of both whole-body tremors and salivation (Shafer *et al.*, 2005). Pyrethroids slow the activation (opening), inactivation (closing) of voltage sensitive sodium channels (VSSC) and shift the membrane potential to more hyperpolarized potentials at which VSSCs open. So,

smaller depolarizing changes in membrane potential activate VSSCs which remain open for extended time so that more Na ions cross and depolarize the neuronal membrane (Fig. 1). The type II pyrethroids postpone the closure of VSSCs for a considerably extended period and membrane potential is depolarized extensively preventing action potentials generation (Shafer *et al.,* 2005).
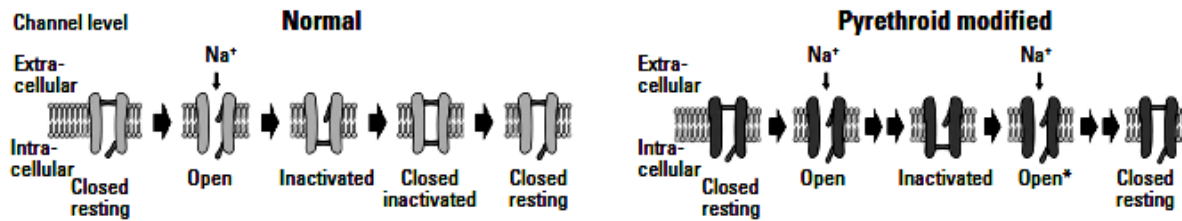
Pyrethroids increase peripheral natural killer and antibody dependent cytotoxicity/immunotoxicity (Madsen *et al.*, 1996; Santoni *et al.,* 1997), embryonic resorption and fetal mortality (Yousef *et al.,* 2003), fetotoxicity (Ahmad *et al.,* 2009), inhibition of Na, K and Mg dependent ATPase activity in liver (Khan *et al.*, 2009) and neurotoxicity (Sharaf *et al.,* 2010). The present review addresses the reproductive toxicology of pyrethroids in non-target species especially mammals. Reproductive toxicology is the study of occurrence, causes, manifestations and consequences of the adverse effects of exogenous agents on reproduction. Reproductive hazards encompass adverse health effects to the future mother and father (loss of libido, infertility, sterility) as well as to the developing offspring (abortion, fetal or prenatal death and teratogenesis). The potential of pesticides to adversely affect development is determined from studies conducted on animals to meet the regulations in enforcement (Martin *et al.*, 2009). During repeated mitotic and meiotic division, there is frequent cell division and cellular DNA replication in the gametes (spermatozoa, ova) as well as the fertilized ovum and the pre and post-implantation embryos. This is the main reason that the organisms in the initial stages of development are absolutely vulnerable to physical and chemical insult (Zenzes, 2000).

Table 1: Structure of some pyrethroids insecticides used as ectoparasiticides in animals

Allethrin/$C_{19}H_{26}O_3$ (Type I pyrethroid)	Permethrin/$C_{21}H_2OCl_2O_3$ (Type I pyrethroid)
Structure	
http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---A/Allethrin.htm	http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---P/Permethrin.htm
Uses Against insects in animal houses and as ectoparasitiside in animals	

Cypermethrin/$C_{22}HCl_2NO_3$ (Type II pyrethroid)
Structure
http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---C/Cypermethrin.htm
Uses   Against ectopararsites. Pour on: 15g/L or 0.15-0.75g/animal in cattle; 2.5g/L or 0.25-0.5g/animal in sheep. Dip for sheep and spray for poultry: 0.1mg/animal (Anonymous, 2001)

Cyhalothrin/$C_{24}H_{25}NO_3$ (Type II pyrethroid)
Structure
http://www.chemicalbook.com/ChemicalProductProperty_EN_CB7377945.htm
Uses   Livestock especially cattle and sheep against ectopararasites. Pour-on cattle: 1.2g in 60mL for ticks and 0.2g in 10mL for lice and fleas, sheep: 0.1g in 5mL for all applications. Cyhalothrin 20% w/v spray is diluted 0.002% to 0.2% and applied as spray or dip and repeated after 3 weeks (Anonymous, 2001).

Deltamethrin/$C_{22}H_{19}Br_2NO_3$ (Type II pyrethroid)
Structure
http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---D/Deltamethrin.htm
Uses   Dip/Spray/Pour-on against ectoparasites: All ruminants: 0.4-1.6mg.kg⁻¹bw. Twice at weekly interval (Anonymous, 2001)

Fenvalerate/$C_{21}H_{25}NO_4$ (Type II pyrethroid)
Structure
http://en.wikipedia.org/wiki/File:Fenvalerate.png
Uses   Ectoparaciticide in cattle and other livestock applied as pour-on at dose of 4 mg.kg⁻¹ bw upto a maximum of 1.6g per animal (Anonymous, 2001)

mg.kg⁻¹ bw: milligram per kilogram body weight.

Fig. 1: Normal structure of voltage sensitive sodium channels (VSSCs). Depolarization opens VSSCs and sodium enters the cell. To limit sodium entry and depolarization length, VSSCs inactivate and must return to a "resting" state before reopening. Pyrethroids delay inactivation of VSSCs and allow continued sodium flux i.e., closed resting state remain opened and inactivation is not carried out (Shafer *et al.,* 2005).

Classical type I (fertility/reproduction) studies use groups of either male or female test rabbits, which are exposed to the test agent with a series of dosages (usually 3 levels) for one gametogenic cycle (60-80 days for the male or about 15 days for the female) and then allowed mating with the opposite partners. If treated female animals are allowed mating with normal untreated males, the pregnant females continue to receive the treatment for either the duration of the gestation or beyond parturition during breastfeeding to their offspring. Males can be treated with an active mutagenic agent and allowed mating with normal untreated females to test the chemical sensitivity of the germ cells *in vivo* at various phases (premeiotic, meiotic, postmeiotic) of spermatogenesis (McClusky, 2008). Mostly adult males are subjected to multiple exposures to various pesticides and other toxins and carcinogens such as diesel fumes and cadmium.

Teratogenicity or developmental toxicity is comprised of the unfavorable effects on the conceptus, starting from initial steps of fertilization to the final achievement of morphological organization and functional potential of the subject (Brannen *et al.*, 2010). The gametes (spermatozoa, ova), the fertilized ovum and the pre and post-implantation embryos are sensitive to exceptionally low concentration of toxic agents. Toxicity at the pre and post-implantation embryo may be elicited as embryo lethality or mild to severe dysmorpho-genesis in organ system(s). The dysmorpho-genesis results in structural deformities, functional and biochemical alterations as well as psychosomatic, behavioral and cognitive insufficiencies at the time of delivery or in a definite postnatal stage. In the past, mostly emphasized to examine the effects of toxic agents on the female to study her role as the vehicle for the susceptible, developing embryo. Such type of study is called segment II or teratogenic study (Ahmad, 2010).

Metabolism of xenobiotics into the metabolites is a two-step process; the phase I carries out their hydrolysis/oxidation/reduction mainly through cytochrome P450 enzyme, whereas in the phase II hydroxyl group (introduced in the phase I) is conjugated with charged amino acid/sulfate/methyl groups (Kumar *et al.*, 2007). Enzymes involved in xenobiotic metabolism are also involved with steroidogenesis. Such enzyme regulation of steroid hormones has made them susceptible to xenobiotics such as pyrethroids. For example some phase I metabolized estrogens have been detected in certain tumors. Catalyzing activity of metabolizing enzymes is distributed by some xenobiotics such as pyrethroids. For instance oxidase cleaves the ester bond of parent pyrethroid for cis-disturbed

cyclopropane of permethrin, while for trans-position an esterase is involved. In case of cypermethrin both isomers need esterase for hydrolysis (Holden, 1979). In either case, due to oxidative stress reactive oxygen species are produced which can cause cellular damage (Shashikumar and Rajini, 2010).

Current experimental and clinical studies with animals demonstrated pyrethoids to hamper endocrine functions (Sun *et al.*, 2007). Study of compounds which are suspected to be endocrine disrupters requires comparative evaluation of structural and biochemical changes produced by them in the body. Among such parameters include measurements of levels of various hormones and enzymes and intermediate metabolites of the compounds (Kumar *et al.*, 2007). Therefore effects of pyrethroids on steroid hormones and their enzymes/ receptors have been addressed in this article. Similarly various pathological effects of pyrethroids on reproductive performance of non-target species of animals have been reviewed and possible pathogenesis for those effects has been suggested in this article. Histo-pathological effects of pyrethroids on testes and epididymis have been correlated with altered sperm characteristics and reductions in sperm counts, testosterone concentration and fertility. The reduced fertility in pyrethoid exposed female animals has also been discussed with relation to pathological effects on uterus, ovaries and hormonal influences. A brief account of teratogenecity and fetotoxicity effects of pyrethroid exposed animals has also been presented.

Presentation of Experimental and Clinical Studies: The modern gene technology has made possible the study of structure and function of steroid receptors (Gustafsson *et al.*, 1990). This subgroup of nuclear receptors is comprised of estrogen receptor, endrogen receptor, thyroid hormone receptor, retinoic acid receptors and orphan (unknown) ligand receptors. The characteristically conserved nuclear receptor region is DNA binding domain (DBD). Proteins on the carboxy terminous bear ligand binding domain (LBD), which is another significant region of nuclear receptors (Truss and Beat, 1993). Studies using receptor mediated luciferase gene assays have speculated that variety of pyrethroids and their metabolites disrupt the function of multiple nuclear hormone receptors and thus have the potential to affect the endocrine and reproductive functions in humans (Du *et al.*, 2010). Postnatal oral administration of 20 mg kg-1 cypermethrin to adolescent male ICR mice increased hepatic activities of antioxidant enzymes but decreased

transcription levels of key genes in pathways of cholesterol synthesis and transport and testosterone synthesis. These include including 3-hydroxy, 3-methyl glutaryl coenzyme A (HMG-CoA) synthase, steroidogenic acute regulatory protein (StAR) and cytochrome P450 17α-hydroxysteroid dehydrogenase (P450 17α) in the liver and testes (Jin *et al.*, 2011).

The male infertility and pyrethroid pesticide exposure have been closely associated in various studies (Perry, 2008). Reduced sperm counts in semen or testicular/epididymal tissues of pyrethroid treated rats (Elbetieha *et al.*, 2001), humans (Tan *et al.*, 2002), mice (Zhang *et al.*, 2007) and rabbits (Ahmad, 2010) have been reported (Table 4). The fecundity/pregnancy rate and reproduction were tremendously influenced with exposure of adult male animals to the pyrethroid, cypermethrin (Elbetieha *et al.*, 2001). The pyrethroid cyhalothrin in male rats was reported to had severely impaired the sexual competence without any treatment related effect on fertility (Ratnasooriya *et al.*, 2002). Pyrethroid exposure in various animals has been reported to decrease testicular sperm counts (Alhazza and Bashandy, 1998; Elbetieha *et al.*, 2001; Zhang *et al.*, 2007). The findings of sperm parameters in various pesticide exposed animals and those reported by studies carried out in insecticide sprayers (Kamijima *et al.*, 2004; Perry *et al.*, 2007) have been found to be compatible (Table 5). Pyrethroids are harmful to integrity of sperm DNA and quality of semen (Ji *et al.*, 2011). The serum testosterone and/or testicular testosterone concentration has been reported to be decreased in pyrethroid treated rats (Elbetieha *et al.*, 2001), rabbits (Yousef *et al.*, 2003) and mice (Wang *et al.*, 2010). Abnormal or dead spermatozoa in mice and rats were reported after exposure to various pyrethroids i.e., cypermethrin (Bunya and Pati, 1988), deltamethrin (Bunya and Pati 1990) and fenvalerate (Pati and Bunya 1989). Testes in pyrethroid treated animals were reported to be atrophied and have islands of haemorrhage at areas surrounding seminiferous tubules indicated by the presence of red blood cells in the interstitial tissue (Elbetieha *et al.*, 2001). Reduced or degenerated seminiferous tubules (Elbetieha *et al.*, 2001; Zhang *et al.*, 2007) with fibrosis (Elbetieha *et al.*, 2001; Sakr and Azeb, 2001) have been documented in testes of pyrethroids treated animals (Table 2). Alhazza and Bashandy (1998) reported swollen fibrocytes in the testes of rats treated with permethrin. Sakr and Azeb (2001) reported that with pyrethroid treatment, seminiferous tubules became hyalinized and thickened with deformed Leydig cells during the study. At the end of the study there were large vacuoles between tubules with degenerated or poorly developed Leydig cells. Deformed Leydig cells were also reported by Alhazza and Bashandy (1998) due to the pyrethroid inhalation in rats. Large number of premature spermatids (Elbetieha *et al.*, 2001), degenerated spermatogenic layers, pyknosis of spermatogonia (Alhazza and Bashandy 1998) and exfoliated germ cells leading to reduction of germ cells (Sakr and Azeb, 2001) have been reported in various animals after treatment with pyrethroids. Sakr and Azeb (2001) narrated that exfoliation of germ cells was time-dependent; moreover, it was accompanied by deformed spermatids and spermatocytes. Zhang *et al.* (2007) reported lack of germ

cells in the testes of pyrethroid exposed mice. Abnormalities in the sperm morphology such as sperm head abnormalities have been documented in various animals in dose dependent manner after thier treatment with cypermethrin (Bunya & Pati, 1988; Venkateshuwarlu *et al.*, 1997; Kumar *et al.*, 2004; Ahmad *et al.*, 2009). Few studies have reported histological alterations in ovaries and uteri of pyrethroiod treated animals (Table 3).

An increase in embryonic resorptions (Rustamov and Abbasov, 1994) and decrease in mating index, implantation sites and foetuses recovered (Elbetieha *et al.*, 2001) were reported in the dams allowed mating with male rats which were treated with different pyrethroids. Gill *et al.* (2011) explored toxic effects of cypermethrin on bovine CLs in vitro, which included vacuolation, necrosis and significantly decreased viable cell counts and progesterone concentration. Pyrethroids have been reported to be capable of disrupting endocrine functions and calcium homeostasis in ovary (He *et al.*, 2006). Microscopic studies of uterus revealed atrophy of endometrial glands in pyrethroid exposed non-pregnant animals (Ahmad, 2010).

Pyrethroids also lead to teratogenecity or reproductive toxicity (Table 5). Tesh *et al.* (1984) in different studies on pregnant female rats found no significant teratogenic effects due to cypermethrin administration during gestation. However, Cantalamessa (1993) and Sheets (2000) reported that baby rats were more sensitive to pyrethroids than mature rats. The above investigators have expressed that ester hydrolysis was an important pyrethroid detoxification reaction in the adult rat. Dose dependent and significantly decreased number of foetuses vs. number of CL (embryonic resorption) and dose dependently increased foetal mortality (Biernacki *et al.*, 1995; Ullah *et al.*, 2006) along with delayed ossification of bones (Biernacki *et al.*, 1995) have been documented when cypermethrin was administered in female rabbits during gestation. Decrease in the implantation sites, corpora lutea and recovered foetuses from uterine horns and increased incidence of pre- and post-implantation losses and early mortality rate in pyrethroid exposed animals have been reported (Shukla and Taneja, 2002; Ullah *et al.*, 2006; Ahmad, 2010).

Andrade *et al.* (2002) investigated the effects on reproductive endpoints of male offspring after administering deltamethrin (0, 1.0, 2.0, and 4.0 mg.kg-1) orally to female rats (n = 10–12/group) daily from day 1 of pregnancy to day 21 of lactation. Fertility, sexual behavior, organ weights, sperm counts/motility, testosterone and histology of testes were examined on adult male offspring. Testicular and epididymal absolute weights and the diameter of seminiferous tubules in the group treated with the highest dose of deltamethrin (4.0 mg/kg) were decreased. Izaguirre *et al.* (2000) observed cypermethrin induced apoptosis in the telencephalon of Physalaemus biligonigerus tadpoles (Anura: Leptodactylidae). Anwar (2003) reported defective physical features in chicks, which were exposed to cypermethrin during incubation. Bouwman *et al.* (2006) determined different pesticides in 152 milk samples from breastfeeding women of three towns in South Africa. Whole milk levels of DDT were highest in primiparae (238.23 mg.L^{-1}), but those of pyrethroids were the highest

in multiparae which included permethrin (14.51 mg.L^{-1}), cyfluthrin (41.74 mg.L^{-1}), cypermethrin (4.24 mg.L^{-1}) and deltamethrin (8.39 mg.L^{-1}). These residue levels of pyrethroids in milk samples especially in multiparae women imply that human infants and neonates are at risk to pyrethroid exposure. The National Teratology Information Service in the UK had obtained follow up data on the outcome of pregnancy in 48 women exposed to pyrethroids during pregnancy. There were 41 normal babies, two spontaneous abortions and five children with different anomalies (Schaefer, 2001).

Pathogenesis: First step in the steroidogenesis in testes is removal of cholesterol in lipid deposits from mitochondria in the Leydig cells. Peripheral benzodiazepine receptor (PBR) and steroidegenic acute regulatory genes are important at outer mitochondrial membrane during this cholesterol transfer (Zhang *et al.,* 2007). The mRNA expression levels of PBR as well as those of StAR were decreased in animals exposed to various pyrtehoids (Zhang *et al.,* 2007; 2008a; Jin *et al.,* 2011). At the inner mitochondrial membranes of Leydig cells cholesterol changes to pregnenolone with the help of P450scc. The protein expression levels of this enzyme were decreased in pyrethroid exposed animals (Zhang *et al.*, 2007). Such results of studies with pyrethroids in animals have been speculated to be due to mitochondrial membrane damage. Cholesterol itself can be synthesized in the body for use in steroidogenesis, which requires HMG-CoA synthase and HMG-CoA reductase in cytosol of Sertoli and Leydig cells (Zhang *et al.,* 2007). Both of these enzymes were reduced in studies on animals undergoing pyrethroid exposure (Zhang *et al.*, 2007; Jin *et al.*, 2011). Cholesterol can also be provided by uptake from blood of both high

(HDL) and low density lipoproteins (LDL). About 70 % of cholesterol transport is carried out through LDL receptoprs (Kumar *et al.,* 2007). In pyretehroid exposed rodents LDL-R mRNA levels tended to be decreased (Zhang *et al.*, 2007; Jin *et al.*, 2011). Figure 2 displays some important events during cholesterol synthesis using the above enzymes/receptors (Kumar *et al.,* 2007).

The reduced sperm counts might be caused by a direct effect of the pyrethroids on testicular Leydig and sertoli cells, causing a decrease in testosterone production (Elbetieha *et al.,* 2001). Pyrethroids cause DNA damage, so there is first increase of sperm head abnormalities and later degeneration and then death of sperms (Ahmad *et al.*, 2009). Another possibility leading to low sperm count is that pyrethroids interact competitively with androgen receptors and sex hormone binding globulins causing disruption of endocrine system by mimicking the effect of female hormone estrogen, leading to low sperm counts (Yousef *et al.,* 2003). The significant reduction in epididymal sperm counts of treated mammals might be important factor for lowered fertility observed in untreated females allowed mating with pyrethroid exposed males. The abnormal testes might be another factor further exaggerating the fertility loss. The pyrethroids decrease the levels of P450scc (cytochrome P450 side chain cleavage) testicular protein and mRNA levels of steroidogenic acute regulatory (StAR) protein in testes (Zhang *et al.,* 2007). Acute regulatory protein of steroidogenic origin and enzymes concerned with the biosynthesis of testosterone are essential for smooth functioning of Leydig cells (Wang *et al.*, 2010). Decreased levels of such agents in CY-treated animals might be hampering the process of spermatogenesis, lowering the level of testosterone and thus causing loss of fertility.

Table 2: Histological lesions in testes of pyrethroid–exposed non-target species of animals

Treatment	Histological Lesions in testes	References
Rat; Inhalation of permethrin	Deformed Leydig cells, pyknosis of spermatogonia, degenerated spermatogenic layers, swollen fibrocytes	Alhazza and Bashandy (1998)
Rat; CY: 13.15 to 39.66 mg/ rat/day	12 wk treatment produced atrophied testes with interstitial haemorrhages, immature spermatids and fibrosis	Elbetieha *et al.* (2001)
Rat; Inhaled 1 ml 0.2% tetramethrin spray every two days (6 wk)	Connective tissue stroma around the seminiferous tubules became loosely packed (at 2 wk), hyalinized and thickened (at 4 wk) and highly degenerated (at 6 wk). The germ cells were first exfoliated then markedly reduced and deformed.	Sakr and Azab (2001)
Mouse; 0, 35 or 70 mg.kg^{-1} cis-per-methrin for 6 wks	A few abnormal seminiferous tubules with vacuoles or lack of germ cells were found in the testes of exposed mice	Zhang *et al.* (2007)
Rat; α-CY @ 5, 10, 25 and 50 mM in normal saline intradermally	Defected germinal layers in the testis	Muthuvivegnandavel *et al.* (2008)
Goat; CY @ 0, 0.1, 0.4, 0.8 or 1.6% (dip on 0, 15 d)	Degenerative changes and loss of spermatogonia, spermatocyte, Sertoli cells, spermatids, and spermatozoa in seminiferous tubules were dose dependent, connective tissue between seminiferous tubules, impaired spermatogenesis	Ahmad *et al.* (2009)
Rat; 2, 20 and 200ppm for 30, 45 and 60 d respectively (subcutaneous)	Pyknotic nuclei within germ cells, Regressed Leydig cells, Arrested spermatogenesis/hypo spermatogenesis with apoptotic figures or cell fragments into lumina of semineferous tubules, Thickened basement membrane with less interstitial tissue and Leydig cells	Issam *et al.* (2009)

CY = cypermethrin; α-CY = alpha cypermethrin; d = day(s); wk = week(s); ppm = parts per million.

Table 3: Histological lesions in ovaries and uteri of pyrethroid–exposed non-target species

Species/Treatment	Histological Lesions	References
Rat; Fenvalerate @ 31.8 mg.kg^{-1} b. wt. p-o (4 wk)	Expansion of endoplasmic reticulum in corpus luteum cells, vacuolization and cristae loss in mitochondria in corpus luteum cells.	He *et al.* (2006)
Rabbit; CY @ 25, 50, 75 mg.kg^{-1} b. wt. i-p on 5th, 10th, 15th and 20th d post-mating	Connective tissue proliferation in the cortex of ovaries and glandular atrophy, congestion and sloughing of epithelium along with connective tissue proliferation in the uterine tissue	Ullah *et al.* (2006)

CY = cypermethrin; α-CY = alpha cypermethrin; d = day(s); p-o = per oral; wk = week(s).

Table 4: Fertility/reproduction toxicity of pyrethroid–exposed non-target species of animals

Species/Sex/Treatment	Reproductive toxicity	References
Mouse; malathion, carbaryl, cypermethrin	Significant abnormalities at $1/10^{th}$ and $1/5^{th}$ doses of LD_{50} in the sperm morphology (24 h and 7 d)	Venkateshuwarlu et al. (1997)
Rat; cypermethrin 34 mg.kg^{-1}	Embryonic resorption in dams mated to CY treated males (2 month pre-mating) was 20 % at high dosage	Rustamov and Abbasov (1994)
Rat; cypermethrin: 39.66 mg/rat/day (12 wk)	Implantations/viable fetuses/ epididymal/testicular sperm counts decreased with pre-mating treatment.	Elbetieha et al. (2001)
Rat; cyhalothrin: 63/100 mg.kg^{-1} (7 d)	Impaired sexual competence (libido, sexual motivation and sexual vigor)	Ratnasooriya et al. (2002)
Mouse; cypermethrin 80 mg.kg^{-1} in corn oil.	Reduction in the number of total implants and significant postimplantation losses	Shukla (2002)
Human (pesticide workers, office workers)	Significantly decreased sperm count in exposed workers than non-exposed workers.	Tan et al. (2002)
Mouse; permethrin @ 35, 70 mg.kg^{-1}	Caudal epididymal sperm count significantly reduced during 6 weeks treatment	Zhang et al. (2007)
Mouse, cypermethrin: 10 mg.kg^{-1} p-o (4 wks)	Delayed pinna detachment/down appearance/eye opening; less development of reflexes	Farag et al. (2007)
Human (male); pesticide sprays	The higher exposure group had lower sperm concentration in urine/semen	Perry et al. (2007)
Rat; fenvalerate: 40mg.kg^{-1} in corn oil (3 d)	Testicular and epididmai sperm counts decreased	Arena et al. (2008)
Rat;1-64mmol.L^{-1} fenvalerate	Reduced sperm motility in vitro in a time (1/2/4h) and concentration dependent manner	Song et al. (2008)
Rat; Different pyrethroids @ 50 mg.kg^{-1} (7 d)	Hershberger assay ranked antiandrogenic activities in as: β-cypermethrin<permethrin<β-cyfluthrin< cypermethrin<cyfluthrin<bifenthrin<flutamide	Zhang et al. (2008b)

d = day(s); wk = week(s); ppm = parts per million; i-p = inraperitoneal; p-o = per oral; LD_{50} = median lethal dose/Lethal Dose, 50%.

The spermatozoa pass through the androgende- pendent organ epididymis for maturation (Mably et al., 1992). Spermatozoal maturation involves an exceedingly complicated and delicately tuned relationship amid spermatozoa and epididymal epithelium (Moore et al., 1998). If the movement of the spermatozoa is accomplished hurriedly, maturation may not be concluded. The altered sperm characteristics due to pyrethroid exposure have been reported to result in unwholesome fertilized ova (Elbetieha et al., 2001) leading to significantly increased resorption in untreated female mammals allowed mating with males exposed to pyrethroids (Farag et al., 2007; Ahmad, 2010). Resorption might be credited to enhanced pre-implantation losses due to hampered fertilization as pyrethroids induce DNA damage, which could occur due to free radicals generation (Aslam et al., 2010). Decreased number of fetuses recovered (Elbetieha et al., 2001; Ahmad, 2010) and implantation sites in untreated female mammals (Shukla and Taneja, 2002; Ahmad, 2010) have been recorded. Dominant lethal mutations induced by mutagenic activity in sperms of CY treated animals are responsible for implantation losses (Shukla and Taneja, 2002).

Endometrial glandular atrophy is reported in uteri of pyrethroid exposed animals and in endometrial biopsies from infertile and repeat breeder animals (Garoussi et al., 2010). Changes at molecular level have been suggested to be responsible for decreased number of implantations. Changes in both endoplasmic reticulum (ER) and mitochondrion in rat ovarian corpus luteum cells after a four-week fenvalerate exposure have been reported (He et al., 2006). Increase in serum free calcium concentration was also reported with pyrethroid exposure. ER accumulates calcium by Ca++ pump, then either inositol 1, 4, 5-trisphosphate or cyclic adenosine diphosphate ribose cause release of Ca++. Calcium can mediate various physico-chemical actions (neurotrans- mitter release, steroidogenesis, fertilization, and DNA synthesis).

Calcium and calcium-calmodulin systems are involved in the gonadotropic regulation of granulosa cell steroidogenesis during follicular development (He et al., 2006). In this way, pyrethroids might be responsible for disturbed ER and mitochondrial functioning in the ovaries and thus fertility loss.

The exposure of pregnant animals to pyrethroids decreased fertility and produced foetal mortality (Ahmad, 2010). Prevention of early implantation and mid-gestation pregnancy termination has been reported with a progesterone antagonist, which induced foetal expulsion despite the high progesterone levels in canines and rabbits (Ozalp et al., 2010). The logic behind the use of abortifacients is that a new pregnancy cannot be established during an ongoing pregnancy. It means that administration of estrogen or progesterone (hormones naturally produced in pregnant animals) or their antagonists will prevent ovulation and implantation (Ozalp et al., 2010). The binding of natural pyrethrins and pyrethroids to receptors of steroid hormones has been documented (Yang et al., 2009). In vivo (Zhang et al., 2008b) and in vitro (Gill et al., 2011) effects of pyrethroids on pregnancy hormones have been reported, so abortifacient role of pyrethroids can not be excluded. Another steroid testosterone in blood plasma/serum of pyrethriood exposed animals was decreased (Elbetieha et al., 2001; Yousef et al., 2003; Wang et al., 2010). However, LH levels are increased in such animals. Such trend might be due to normal negative feed back in response to the decreased testosterone hormone of the hypothalamus-pituitary axis (Zhang e et al., 2007).

The reduction in the size of chick head of pyrethroid exposed embryos reflected the reduction in the size of brain that occurred as a result of degenerative changes in neurons, which in turn might have occurred as a result of pyrethroid induced apoptosis (Anwar, 2003). Farag et al. (2007) commented that maternal toxicity could be the

trigger for the decreased pup weight gain and delayed development of physical features in the high dose group (50% of the control). The undersized progeny might have developed alterations in neuromuscular parameters afterwards. It has been quoted that the higher level of sensitivity of the neonatal mammals to pyrethroid toxicity might be due to partial ripeness of the enzymes which catalyze the pyrethroids metabolism in the liver of juveniles (Cantalamessa, 1993; Farag *et al.,* 2007). Moreover, during organogenesis fetuses suffered toxicity but pyrethroid treatment during the maturation phase did not significantly produce reproductive toxicity (Syed *et al.,* 2010). It might be because fetuses which survived up to advanced stage might have recovered from mild lesions developing at earlier stage. It has been reported that there is rapid DNA repair in late embryo stages, but early embryo stages are more likely to develop toxicity (Hook and Lee, 2004).

Increased catalase activity and reduced superoxide dismutase, glutathione preoxidase, vitamin E and vitamin C activities in pyrethroid treated animals have been documented to be maintained normal by vitamin E supplementation (Raina *et al.,* 2009; Aslam *et al.,* 2010; Sharaf *et al.,* 2010; Navayath and Thiyagarajan, 2011). Furthermore, α-tocopherol supplementation in the spring season increased the spermatozoal plasminogen activator activity in rams (Rekkas *et al.,* 2000). Such reports suggest that vitamin E could have a protective role in pyrethroid induced oxidative stress and reproductive toxicity in animals (Yousef *et al.,* 2010). However, a negative correlation between vitamin E with steroids and their binding proteins has been reported selectively in smokers, which imply that vitamin E may be a risk factor for prostate cancer in smokers (Mondul *et al.,* 2011). In general vitamin E has a protective effect on Leydig cell steroidogenesis. In vitro and in vivo studies on young adult Brown Norway rats suggested that vitamin E suppress Fe2+/sodium ascorbate-induced lipid peroxidation in Leydig cells. Thus Leydig cell do not stop steroidogenesis due to production of reactive oxygen species (Chen *et al.,* 2005).

Conclusions

The pyrethroids lead to reduction in sexual competency, reproductive efficiency and fertility in both sexes of non-target species of animals. Adverse effects on the earlier stages of life in terms of teratogenecity and fetotoxicity are also important concern of pyrethroid toxicity. Therefore, over-dosage of pyrethroids must be avoided at any cost. Furthermore, vitamin E supplen- tation might be helpful in reducing pyrethroid induced toxicity.

Table 5: Teratogenic toxicity of pyrethroid–exposed non-target species of animals

Subject/Treatment	Teratogenecity produced	References
Rat: CY and permethrin used with pretreatment of piperonyl butoxide (PB), or tri-o-triolyl phosphate (TTP)	Lethal pyrethroid effects not altered significantly by drug inhibitors in the neonatal rats, but in adults, esterase inhibitor (TTP) increased pyrethroid toxicity.	Cantalamessa (1993)
Rabbit; CY @ 1000 mg.kg⁻¹ (28 d)	Embryonic resorption and foetal mortality along with delayed ossification of bones	Biernacki *et al.* (1995)
Rat; cismethrin, permethrin, deltamethrin or CY	Young rats more sensitive than adults to lethal doses of pyrethroids	Sheets (2000)
Chick embryo; cypermethrin 50, 100, 200 and 400 ppm (single dose) at 0 day of incubation	Reduced size of head, brain, eyeballs and crown rump length; incomplete development of eyes, beak and wing buds; micromelia, exocardiogenesis on day 7 of incubation	Anwar (2003)
Rabbit; Cypermethrin: 25, 50, 75 mg.kg⁻¹ i-p 5/10/15/20d post-mating	Dose dependent and significantly decreased number of foetuses vs. number of CL. Dose dependently increased foetal lethality	Ullah *et al.* (2006)

CY: cypermethrin; CL: corpus luteam/corpora lutea
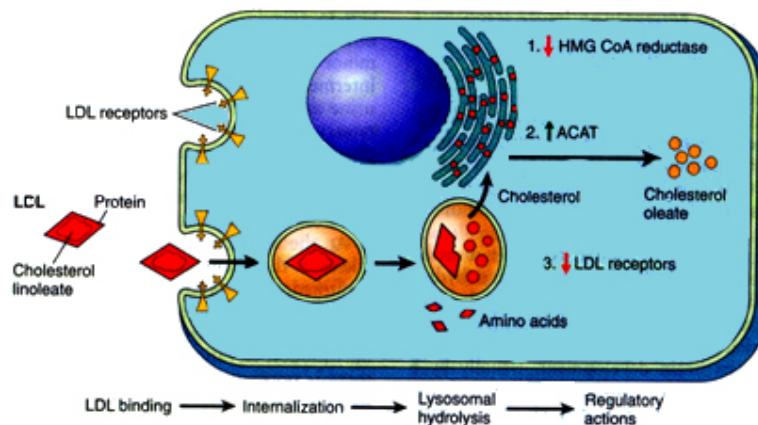
Fig. 2: Low density lipoprotein (LDL) in the mammalian cells undergoes an array of metabolic pathway and free cholesterol accomplishes various functions. Arrow (1) indicates that decreased expression of HMG-CoA reductase inhibits the cholesterol synthesis. Arrow (2) indicates that activation of ACAT leads the excess cholesterol to be stored through esterification. Arrow (3) indicates the down regulation of LDL receptors by cholesterol to prevent excessive cholesterol accumulation in cell (feedback inhibition). ACAT: Acyl Co-A-cholesterol acyl-transferase; HMG-CoA reductase: 3-hydroxy, 3-methyl-glutaryl coenzyme A reductase (Kumar *et al.,* 2007).

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