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Review Article

Hemato-Biochemical Changes Induced by Pyrethroid Insecticides in Avian, Fish and Mammalian Species

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ABSTRACT

Agricultural pests and ectoparasites in animals/poultry are controlled by spraying pesticides/insecticides which include pyrethroids, organophosphates, carbamates and organochlorines. Pyrethroids having high efficiency with low toxicity to mammals and easy biodegradability are preferred over other insecticides. Cypermethrin, type II synthetic pyrethroid is extensively used in Pakistan, as it is considered as safer to the public health point of view than the other insecticides in the market. The chronic use and excessive doses of pesticides like pyrethroids may, however, become part of food chain leading to a series of hematological, biochemical, reproductive and pathological changes in the body. This review deals with the hematological and biochemical alterations rendered by pyrethroids in mammals, fish and birds. © 2012 Friends Science Publishers

Key Words: Pyrethroids; Hematology; Biochemistry; Toxicity; Pesticides; Mammals; Fish; Birds

INTRODUCTION

Insecticides, fungicides and herbicides constitute the major source of potential environmental hazards not only to birds, fish, and other animals but also to humans when they become part of food chains (Abd-Alla *et al*., 2002). Long term exposure to these products causes countless abnormalities and reduces the life span of organisms (Hussain *et al*., 2011; Naz *et al*., 2011).

Various chemicals have been used as insecticides/pesticides in public health programs, veterinary and agriculture. Use of pesticides having acute toxicity is prohibited; however, pyrethroids are extensively used in Pakistan (Aslam *et al.,* 2010; Ahmad *et al.,* 2011). Pyrethroids are preferred above organophosphates, carbamates and organochlorines as these have high efficiency, low toxicity and easy biodegradability (Sharaf *et al*., 2010). For more than 30 years, pyrethroids are in use for home formulations and agricultural purposes and these insecticides cover nearly one-fourth of the worldwide market (Ahmad *et al*., 2012b). In the last decade, their use has been increased (Bhushan *et al*., 2010). Cypermethrin (CY), type II synthetic pyrethroid, lipophilic in nature, is considered to be less toxic due to its speedy insect killing properties and having low toxicity to mammalian tissues (Aslam *et al*., 2010). However, it is abstemiously toxic when applied dermally or administered orally (Luty *et al*., 1998; Aslam *et al*., 2010).

Poultry industry plays an important role in producing animal proteins most effectively and economically within the shortest possible time (Hosseinzadeh *et al*., 2010) and provides good employment sources (Ghafoor *et al*., 2010; Mahmud *et al*., 2011). Likewise, small and large ruminants also play an important role in the production of meat, wool and hides. These species suffer from ectoparasites (Irshad *et al*., 2010), if these are not treated, consequences appear in the form of blood loss, lowered immunity (Siddiki *et al*., 2010; Abubakar *et al*., 2011; Ehtisham *et al*., 2011), lowered egg production (Mahmud *et al*., 2011), reduced birth weight, behavioral changes; such as excessive scratching, weight loss (Eo & Kwon, 2010), decreased weight gain, and decreased milk production (Ahmad *et al*., 2009a). Similarly, vegetables and grain crops are extensively sprayed with pesticides to increase production (Iqbal *et al*., 2010; Hafeez *et al*., 2010; Naseer-ud-Din *et al*., 2011). If these pesticides are used in excessive dosage, then these become part of food chain, triggering a series of hematological (Atamanalp & Yanik, 2003; Ahmad *et al*., 2009a; Hussain *et al*., 2011), biochemical (Atamanalp *et al.,* 2002; Naz *et al*., 2010; Hussain *et al*., 2012), reproductive (Ahmad *et al*., 2009b; Ahmad *et al*., 2012a), pathological changes (Bhushan *et al*., 2010; Ahmad *et al*., 2011; 2012b), and lead to abnormalities in respiratory, nervous, immune and endocrine systems (Naz *et al*., 2010), Annually, more than 25-77 million poisoning cases (Zhang *et al*., 2011) and 0.22 million casualties (Yashmashito *et al.,* 1997) due to pesticide poisoning have been reported, especially in third world nations (Ahmad *et al*., 2009b). This review is an update of the hematological and biochemical alterations rendered by pyrethroids in mammals, fish and birds.

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Hematological Changes

Changes in hemogram: Blood findings are important for the assessment of various systemic functions and health of animals under various environmental conditions and most importantly, for diagnosis of drug or chemical induced hemolysis (Atamanalp & Yanik, 2003). Minimum hematological package must include hematocrit (Hct), Hemoglobin (Hb) concentration and Total Erythrocyte Counts (TEC); these parameters have been frequently included in toxicological studies (Gad & Chengelis, 1988). However, information regarding hematological alterations following exposure to CY is inconsistent. It might be partially due to various non-specific features influencing hematological parameters. These features may include alterations in circulations, rate of food consumption, fluid and salt balance, food utilization, and feeding pattern. Venipuncture and blood sampling and experimental variables may also influence hematology (Greaves, 2007).

Some of the reports on pyrethroid induced hematological changes have been summarized in Tables I-II. Experiments conducted by Ishmael and Litchfield (1988) for the feeding permethrin to mice revealed non-significant effect on hematological values. Similarly, no effect of sex was seen in rats fed cyhalothrin (EPA, 1985, 1994). According to EPA, statistically significant hematological findings in pyrethroid orally fed animals could be attributed to adaptive reactions rather than persuaded hematotoxicity. However, anemia was reported in mice treated with fenvalerate (EPA, 1991). Decrease in Hb concentrations and TEC in female rats and decrease in Hct in male rats fed CY have also been reported (Anonymous, 1989). Dogs and mice treated with fenvalerate revealed decreased TEC, Hct and Hb (Parker *et al*., 1984; EPA, 1991). Similarly, Shakoori *et al*. (1992) reported significantly decreased TEC, Hb contents, and mean corpuscular Hb (MCH) in rabbits treated with fenvalerate. Evidence of anemia in dogs fed pyrethrins in diet daily for two months is documented (Schoenig, 1995).

It can be interpreted from Table II that CY treated animals were suffering from anemia (Saxena & Seth, 2002; Yousef *et al*., 2003; Shah *et al.,* 2007; Khan *et al*., 2009). Few workers reported non-significant changes in TEC, Hb, and Hct in various animals treated with CY (Shakoori *et al*., 1988; Mansee, 1998; Institoris *et al*., 1999; Haratym-Maj, 2002; Matsushima *et al*., 2003; Sayim *et al*., 2005). Luty *et al*. (2001) reported that deltamethrin and fenvalerate regardless of doses enthused erythropoiesis and synthesis of hemoglobin in male Swiss mice; whereas, in female mice deltamethrin led to anemia which indicated conquest of erythropoiesis and hemoglobin synthesis. Anemia developed in female mice at low CY doses (5 $mg.kg^{-1}$ b. wt.); whereas, at high CY doses (25 $mg.kg^{-1}$ b. wt.) no anemia was observed (Haratym-Maj, 2002). It was hypothesized that female mice could be more sensitive to lower doses of pyrethroids for longer time, which could be related with depressant effect of synthetic pyrethroids on erythropoietin (EPO) hormone which controls erythropoiesis.

Substantial decrease in TEC and hemoglogin could possibly be due to suppression of erythropoiesis and heme synthesis, and also to devastation of erythrocyte in hemopoietic tissue (Manna *et al*., 2004a; Fetoui *et al*., 2008). Erythrocyte lysis is produced by agents those injure the red cell membrane, leading to oxidative damage to hemoglobin or may be suppressing the anti-oxidative protective mechanism. Augmented hemolysis usually lead to reduction in Hb, TEC and Hct and are escorted by elevated reticulocytes counts, amplified anisocytosis, increased red cell dissemination width and volumes.

Significantly increased mean corpuscular volume (MCV) after pyrethroid treatment was reported in various animals (Matsushima *et al*., 2003; Sayim *et al*., 2005; Shah *et al*., 2007) at different doses (Table III). Significantly decreased (Matsushima *et al*., 2003) and increased MCH (Sayim *et al*., 2005) after pyrethroid treatment was reported in rats, but MCH was either unaffected (Shah *et al*., 2007) or increased (Basir *et al*., 2011) by the pyrethroid treatment in rabbits. Significantly decreased mean corpuscular Hb concentration (MCHC) after pyrethroid treatment was reported (Matsushima *et al*., 2003; Basir *et al*., 2011). Contrary to the above reports, Sayim *et al*. (2005) and Shah *et al*. (2007) reported no effect of pyrethroid treatment on MCHC (Table II).

Nuclear changes: Insecticides/pesticides have been reported to lead to DNA damage which appears in the form of micronucleus formation, chromosome aberrations and mitotic aberrations (Kocaman & Topaktaş, 2010; Sharaf *et al*., 2010; Sankar *et al.,* 2010; Hussain *et al*., 2011, 2012). Micronucleus appearance in the cytoplasm is considered as biomarker of DNA damage (Saleh & Sarhan, 2007). Micronuclei are of same color, refraction and texture to that of nucleus and appear as separate small nuclei having size of 1/10 in length and 1/3 in diameter of the main nucleus (Fig. 1).

With the treatment of pyrethroids, micronucleus could result when the entire or chromosome fragments are not incorporated in the main nucleus after cell division (Sankar *et al*., 2010). As a result of genetic damage, i.e., damage to the chromosomes, fragments lagging in the course of anaphase or lagging acentric chromosomes or cytoplasmic chromatin-containing bodies are failed to be incorporated into daughter nuclei (clastogenesis), results in the development of micronuclei in red blood cells (Sharaf *et al*., 2010).

Cypermethrin has mutagenic activity like that of numerous pesticides (Sankar *et al.,* 2010; Muranli & Guner, 2011). Due to exposure of these pesticides, micronucleus formation, sister chromatids or chromosomal aberrations have been documented (Kocaman & Topaktaş, 2010). Fastac 10 EC (a pyrethroid) in high concentrations has reported to damage the mitotic spindle, clastogenic activity and amplified occurrence of micro-nucleated in erythrocytes

Table I: Alterations in total erythrocyte counts, hemoglobin concentration, hematocrit and leukocytes as reported by previous workers after CY treatment

Subject	Dose	TEC	Hb	Hct	Leukocytes	Reference
Rat	CY @ 420 mg.kg^{-1} b. wt. (6 mo)	Low	NS	Low	NS	Shakoori *et al*. (1988)
	CY @ 55.4, 22.2, 11.1 mg.kg^{-1} b. wt. (28 d)	NS	Low	NS	Leucopenia	Institoris *et al*. (1999)
	Cyhalothrin @ 100 mg.kg^{-1} b. wt. (7 d)	Low		Low	NS	Ratnasooriya et al. (2002)
	Pyrethroid S-421 @ 640 mg.kg^{-1} b. wt	NS		NS	Leucopenia	Matsushima *et al*. (2003)
	CY @ 14.5 mg.kg^{-1} b. wt. (30 d)	Low		Low	Neutrophilia	Manna *et al*. (2004a)
	CY @ 150 mg.kg^{-1} b. wt. (28 d)				NS	Sayim *et al*. (2005)
	CY @ 300 mg.kg^{-1} b. wt. (28 d)				Leuko-, lympho- and mono-cytosis	
	10 mg.kg^{-1} b. wt.				NS	Mansee (1998)
Mouse	Pyrethroids; @ 2000 mg.kg^{-1} diet	NS	-	NS	Leucopenia, lymphopenia, neutrophilia	Prentice *et al*. (1981)
Female	Deltamethrin @ 5 mg.kg^{-1} b. wt.	Low	Low	Low	Leukocytosis	Luty *et al*. (2001)
Mouse	CY @ 5 mg.kg^{-1} b. wt.					Haratym-Maj (2002)
	CY @ 25 mg.kg^{-1} b. wt.	High	High	High		
Male	CY @ 5, 25 mg.kg^{-1} b. wt.	NS	NS	NS		
Mouse	Deltamethrin @ 5, 25 mg.kg^{-1} b. wt.; fenvalerate @ 10, 50 mg.kg^{-1} b. wt. (28 d)	High	High	High		Luty *et al*. (2001)
	Fenvalerate (7 d) @ 10 mg.kg^{-1} b. Wt.			NS	Leukocytosis	Shakoori *et al*. (1992)
	CY @ 24 mg.kg^{-1} b. wt. (12 wk)				Leukocytosis	Yousef *et al*. (2003)
	Cyhalothrin @ 1, 4, 8 mg.kg^{-1} b. wt. i-p				Leuko-, lympho- and mono-cytosis, neutrophilia,	Basir *et al*. (2011)
Sheep	Dimethoate @ 1.6, 3.2 or CY @ 6, 12 mg.kg^{-1} b. wt. (63 d)				Leukocytosis	Yousef *et al*. (1998)
Rabbit	CY @ 25, 50, 75 mg.kg^{-1} b. wt.				Leuko-, lympho- and mono-cytosis	Shah *et al*. (2007)
Buck	CY @ 0,0.1,0.4, 0.8 or 1.6% at 0 and 15 d				Leukocytosis	Khan *et al*. (2009)
Chick	Fenvalerate @20 ppm for 8 weeks	NS	NS	NS	Leukopenia, heterophilia, lymphopenia	Garg *et al*. (2004)
Fish	CY @ 0.02 ppm (6, 9, 12, 15 hrs)	Low	Low	Low	NS	Dorucu & Gorgon (2001)
	CY @ 0.001, 0.003, 0.005, 0.007 ppm (96 h)				Leukopenia	Çakmak & Gorgon (2003)
	CY; 1/10th and 1/50th of 96 h $LD_{50;}$ (45 d)			NS	Leukocytosis	Das & Mukherjee (2003)
	CY @ 0.16, 0.40, 0.80 µL.L^{-1}			Low	Leukocytosis	Adhikari *et al*. (2004)
Fish	Deltamethrin, 1.61 mu g/L	Low	Low	-	Low	Vani *et al*. (2011)

CY = cypermethrin; d = day(s); h = hour(s); NS = non-significant; i-p = intraperitoneal; mo = month(s); wk = week(s)

Table II: Alterations in erythrocyte indices as reported by previous workers after CY treatment in different species

Species	Dose	MCV	MCH	MCHC	Reference
Rat	Cyhalothrin @ 100 mg.kg^{-1} b. wt. (7 d)	Low	NS	Low	Ratnasooriya *et al*. (2002)
	S-421 (pyrethroid) @ 640 mg.kg^{-1} b. wt.	High	Low		Matsushima *et al*. (2003)
	CY @ 150 mg.kg^{-1} b. wt. (28 d)	High	High	NS	Sayim *et al*. (2005)
Rabbit	Cyhalothrin @ 1, 4, 8 mg.kg^{-1} b. wt. i-p	High	High	Low	Basir*et al*. (2011)
	CY @ 25, 50, 75 mg.kg^{-1} b. wt. (4 injections at 5 days interval.) i-p	High	NS	NS	Shah *et al*. (2007)
Fish	CY @ 0.02 ppm (6, 9, 12, 15 h)	Low	Low	High	Dorucu & Gorgon (2001)
	CY @ 0.001, 0.003, 0.005, 0.007 ppm (96 h)	High	No effect	Low	Çakmak & Gorgon (2003)
	0.16, 0.40, 0.80 µLL-1	High	High	NS	Adhikari *et al*. (2004)

CY = cypermethrin; d = day(s); h = hour(s); NS = non-significant; ppm = parts per million

of tadpoles (Bosch *et al*., 2011). These micronuclei could also take place by the loss of complete or parts of chromosomes at anaphase from daughter nuclei and occur distinctly in the cell from the main nucleus (Sankar *et al*., 2010).

Not only pyrethroids like CY cause DNA damage (Muranli & Guner, 2011) but other insecticides like malathion **(**organophosphate) do cause the same damage (Sarabia *et al*., 2009). Other than the above hypothesis of nuclear changes, these could be due to intracellular generation of reactive oxygen and nitrogenous species (Altuntas & Delibas, 2002).

Other morphological alterations which have been reported due to the treatment of pyrethroids in erythrocytes are pear shape erythrocytes or binucleated erythrocytes (Fig. 2), lobed or notched nuclei along with blebbed membrane nuclei and micronuclei (Fig. 3). These morphological changes could be the result of oxidative damage to mitochondrion. This oxidative damage also pledges the apoptotic changes like production of fodrin proteins and cleavage of cytoskeleton gelsolin and increased caspase activated DNase (CAD) in the nucleus which is responsible for the degradation, breakdown and disintegration of nuclear lamins proteins (Fernandes *et al*., 2007). These nuclear abnormalities could also be due to over generation of caspase activated DNase which is responsible for the cleavage of cytoskeletal (gelsolin, fodrin & vimentin) and nuclear proteins (Banerjee *et al*., 2001). It is alluring to speculate that blebbed, notched and lobed nuclei could result from aneuploidy, i.e., a process leading to formation of chromosomal abnormalities (Çavaş & Ergene-Gözükara, 2005).

The comet assay is another method to observe damaged DNA which appears as a fluorescing material

Table III: Protein and enzyme alterations as reported by previous workers after pyrethroid treatment

Species/Dose	Protein	ALT or GPT	AST or GOT	ALP	LDH	Reference
Rat; CY in feed @ 420 mg.kg^{-1} (6 mo)	High (31%)	-	Low (37%)	-	High (61%)	Shakoori *et al.* (1988)
Rat; CY @ 1600 mg.kg^{-1} feed (3 mo)	-	-	-	High	-	Anonymous (1989)
Rat hepatocytes; CY @ 400, or 800 ng per 2 x 10^6 cells (2 h)	-	Higher (at 2 h male and at ½ h female)	Higher at 30 min	-	-	El-Tawil & Abdel-Rahman (1997)
Rat; Permethrin @ 80-120 mg.kg^{-1} b. wt. (15 d)	NS	High	High	-	-	Shah & Gupta (1997)
Rat; CY @ 14.5 mg.kg^{-1} b. wt. (30 d)	Low (21%)	V. High (121%)	High (21%)	V. High (107%)	High (31%)	Manna *et al*. (2004b)
Rat; 1500 mg.kg^{-1} feed	High	High	-	-	-	Hussain *et al*. (2009)
Rat; deltamethrin @ 1.28 mg.kg^{-1} b. wt. p-o (30 d)	Low (18%)	High (70%)	High (59%)	High (48%)	High (59%)	Yousef *et al*. (2006)
Rat; cyhalothrin @ 612 mg.kg^{-1} b. wt.	-	High	High	-	High	Fetoui *et al*. (2008)
Rabbit; CY @ 24 mg.kg^{-1} b. wt.	-	Low (liver, testes) High (plasma)	Low (liver, testes) High (plasma)	Low (liver) High (plasma)	-	El-Demerdash *et al*. (2003)
Rat; Alpha-CY @ 5, 10, 25 and 50 mM in normal saline intradermally		Low (brain, kidney, testes) High (liver, serum)		High (heart, kidney, testes, serum)		Muthuviveganandavel *et al*. (2008)
Sheep; 6/12 mg.kg^{-1} b. wt. Oral (63 d)	Low	V. low	V. low	V. low	-	Yousef *et al*. (1998)
Ram; 6/12 mg.kg^{-1} b. wt. (63 d)	-	V. High	V. High	-	-	Yousef *et al*. (1999)
Buck; on 0 and 15 day; 0%, 0.1%, 0.4%, 0.8% or 1.6% CY dip	Low	High	High	No effect	-	Khan *et al*. (2009)
Human; spray on indoor walls; deltamethrin @ 20 mg.m^2 and bifenthrin @ 25 mg.m^2 for 6h on d 1-6 and sera collected on d 0, 4 and 7.	Low (on day 4 than day 0)	NS	NS	NS		Srivastava *et al*. (2005)
Human; 0.1% *d-trans* allethrin	NS	High	NS	-	-	Narendra *et al*. (2008)
Rat; Lambda cyhalothrin - 668 ppm p-o daily for 3 wk	-	High	High	-	High	Fetoui *et al*. (2009)
Rat; Lambda cyhalothrin 7.8mg.kg^{-1} b. wt (7/15/30 or 45 d)		High (liver)	High (liver)	-	-	Paliwal *et al*. (2009)
Fish: CY; 0.05 mu g/l	-	High	High	-	-	Firat *et al*. (2011)
Chick; fenvalerate @ 525.6 mg.kg^{-1} b. wt. (28 d)	Low	High	Low	-	-	Majumder *et al*. (1994)
Chick; (6 wk) deltamethrin @ 100 mg.kg^{-1} b. wt.	-	-	High	-	High	Jayasree *et al*. (2003)
Chick egg; CY @ 100, 200, 400 ppm injected at d and 7 of incubation	NS	NS	NS	Low (32, 85, 53% at 3 doses, respectively)	NS	Anwar (2003)
Chick; CY @ 600 mg.kg^{-1} b. wt.	High	High	Low	Low	Low	Aslam *et al*. (2010)
Fish; CY @ 3 µgL^{-1} (5, 10 d)	High	High	High	-	-	Philip & Rajasree (1996)
Fish; CY; 1/10th and 1/50th of 96 h LD_{50} (45 d)	Low	-	-	Low	High (brain, liver); low (kidney)	Das & Mukherjee (2003)
Fish; CY@ 4.1 x 10^{-3} mg.L^{-1} 2.05 x 10^{-3} mg.L^{-1} and 1.025 x 10^{-3} mg.L^{-1}	18.2 % ↑, 4.8 % ↓ and 18.2 % ↑ at three doses.	-	-	-	-	Atamanalp *et al*. (2002)
Fish; fenvalerate (1/3rd of LC_{50})	Low	High	High	-	-	Prusty *et al*. (2011)
Swiss albino Mice; Lambda-cyhalothrin, 100 or 250 mg/kg b. wt	-	High	High	-	-	Çavuşoğlu *et al*. (2011)
Fish; deltamethrin, 1.61 mu g/L	Low	High	High	High	Low	Vani *et al*. (2011)

CY = cypermethrin; d = day(s); h = hour(s); NS = non-significant; mo = month(s); ppm = parts per million; wk = week(s)

around the nuclei, making a tail of variable length along the electric field (Fig. 4). These pesticides not only damage DNA in erythrocytes but also in hepatocytes, lymphocytes, and other cells in the body (Hussain *et al*., 2011; Cortés-Gutiérrez *et al*., 2011).

Changes in leukogram: Leukocytosis has been documented after CY or other pyrethroids treatment in mammals (Shakoori *et al*., 1992), poultry and fish (Table I). Leukocytosis was observed in 15% human cases of pyrethroid poisoning (He *et al*., 1989). Shakoori *et al*. (1992) reported significantly increased white blood cell (WBC) counts in rabbits following daily oral administration of fenvalerate. Contrarily, leukopenia has also been documented after CY or other pyrethroid treatment (Institoris *et al*., 1999; Matsushima *et al*., 2003). Haratym-Maj (2002) suggested that an increase in the number of leukocytes in the blood of animals might result from the mobilization of the immunological system and/or a shift in the leukocytic pool from the spleen to peripheral blood.

Effects of pyrethroid treatment in different animals on differential leukocytic counts included neutrophilia

Table IV: Alterations in albumin, globulin, urea and creatinine concentrations as reported by previous workers after pyrethroid treatmen

Species/Dose	Albumin	Globulin	Urea	Creatinine	Reference
Sheep; 6/12 mg.kg^{-1} b. wt. p-o (63 d)	Low	Low	-	-	Yousef *et al.* (1998)
Chick; deltamethrin @ 100 mg.kg^{-1} feed (6 wk)	-	-	High	High	Jayasree *et al.* (2003)
Rabbit; CY @ 24 mg.kg^{-1} and/or isoflavones @ 2 mg.kg^{-1}b. wt. (12 weeks)	-	-	High	High	Yousef *et al.* (2003)
Rabbit; CY @ 24 mg.kg^{-1} b. wt.	-	-	-	-	El-Demerdash *et al.* (2004)
Rat; deltamethrin @ 1.28 mg.kg^{-1} b. wt. p-o (30 d)	Low: 16%	Low: 25%	High	High	Yousef *et al.* (2006)
Rat; d-trans allethrin 0.2 %w/w mosquito coil smoke for 12 h, 7, 14, 21 and 28 days	-	-	High	High	Garba *et al.* (2007b)
Human; Mosquito coils with 0.1% *d-trans* allethrin, and mats with 1.6% *d-trans* prallethrin	NS	NS	-	-	Narendra *et al.* (2008)
Chick; CY @ 600 mg.kg^{-1} b. wt.	-	-	Low	NS	Aslam *et al.* (2010)
Rat; Lambda cyhalothrin - 668 ppm p-o (3 weeks)	-	-	High	High	Fetoui *et al.* (2009)
Swiss albino Mice; Lambda-cyhalothrin, 100 or 250 mg/kg b. wt	-	-	High	High	Çavuşoğlu *et al.* (2011)
Fish; deltamethrin, 1.61 mu g/L	Low	Low	-	-	Vani *et al.* (2011)

CY = cypermethrin; d = day(s); h = hour(s); NS = non-significant; p-o = per oral; ppm = parts per million; wk = week(s)

Fig. 1: Blood smear from bird treated with cypermethrin showing mature erythrocytes, micronucleus (arrows) and microcyte (arrowhead). Wright-Geimsa stain: Lens 100 X (Sharaf *et al*., 2010)

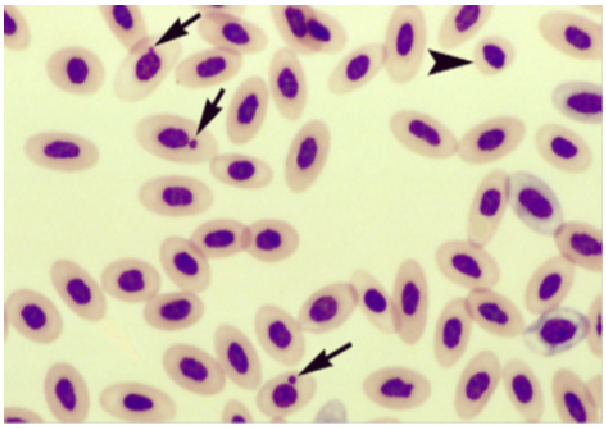


Fig. 2: Micronucleated erythrocyte (MNE) in peripheral blood smear from *Odontophrynus cordobae* (Bosch *et al*., 2011)

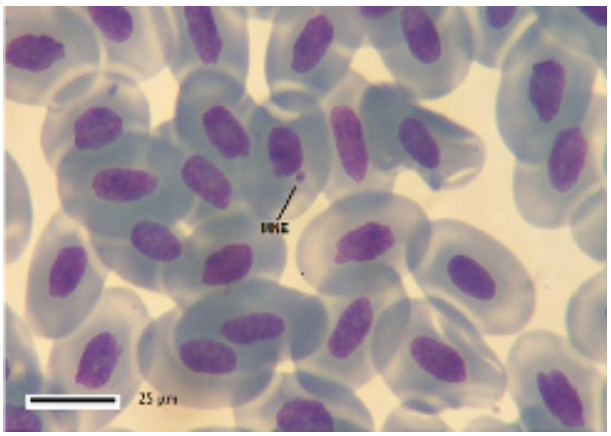


Fig. 3: MN and other nuclear abnormalities. BN: binucleus; BL: blebbed nuclei; LB: lobed nuclei; NT: notched nuclei in peripheral blood erythrocytes of *O. niloticus* (Çavaş & Ergene-Gözükara, 2005)

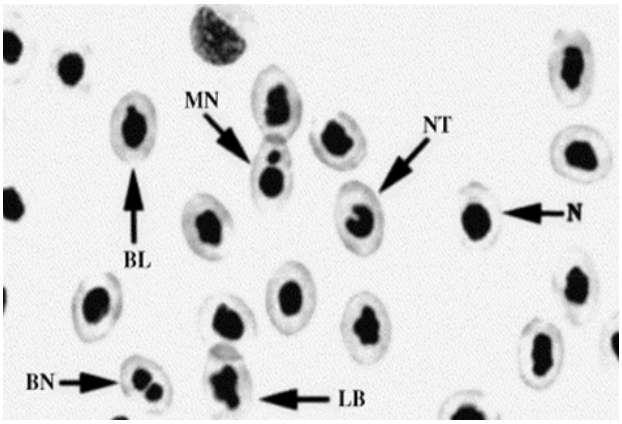
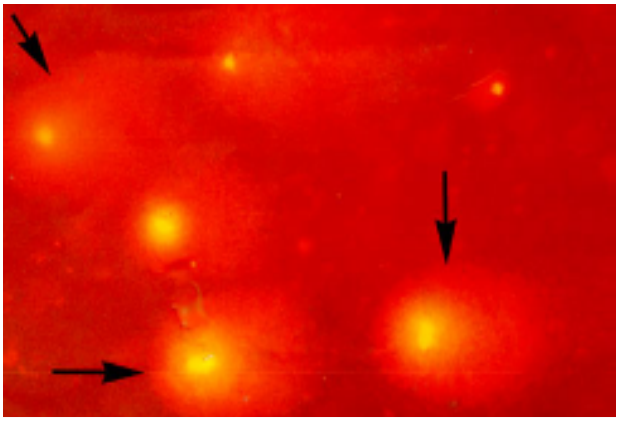


Fig. 4: DNA damaged (comet assay) material fluorescing around the nuclei, making a ‘‘tail’’ of variable length (arrows) (Hussain *et al*., 2011)



(Prentice *et al*., 1981; Manna *et al*., 2004b; Basir *et al*., 2011), lymphocytosis along with monocytosis (Sayim *et al*., 2005; Shah *et al*., 2007) or lymphopenia (Basir *et al*., 2011). Increase of neutrophils represents inflammation in visceral organs (Manna *et al*., 2004b). Many workers, however, reported non-significant alterations in leukocytes with the exposure of different pyrethroids at different dose levels (Shakoori *et al*., 1988; Mansee, 1998).

Biochemical Changes

Changes in proteins: Some of the biochemical findings in CY treated animals published in the accessible literature have been shown in Tables III-IV. Most of the studies revealed decreased proteins in CY treated animals, but Hussain *et al*. (2009) and Aslam *et al*. (2010) reported increased proteins and some other workers (Sayim *et al*., 2005) reported no effect on protein concentration by different pyrethroids (Table III). Khan *et al*. (2009) reported dose dependent decrease in total serum proteins on days 15 and 30 as compared to the control (Table III). They also found decreased concentration (as compared to that of the control) of serum albumin and globulin on day 30 and that of fibrinogen on days 15 to 45 of the experiment (Table IV). Thus, protein concentration might show dose and time dependent changes with pyrethroid treatment. In animals treated with pyrethroids, decrease in plasma proteins, principally albumin could be ascribed to alterations in the metabolism of protein and free amino acid and their production in the liver (Rivarola & Balegno, 1991). Another option for this reduction could be endorsed partially to the harmful result of pyrethroids on hepatocytes as has been established by the increased concentration of ALT, AST and LDH (Yousef *et al*., 2006).

Changes in enzymes: Various studies (El-Tawil & Abdel-Rahman, 1997; Yousef *et al*., 1999; Manna *et al*., 2004a; b; Khan *et al*., 2009; Aslam *et al*., 2010; Ahmad *et al*., 2011) have revealed increased serum activities of leakage enzymes including alanine transaminase (ALT) and aspartate transaminase (AST) in CY treated animals, but few studies (Yousef *et al*., 1998; El-Demerdash *et al*., 2003) claimed the opposite effect; whereas, Srivastava *et al*. (2005) reported no effect of CY on the leakage enzymes (Table III). Yousef *et al*. (1998) reported decreased while Yousef *et al*. (1999) reported increased ALT/AST in sheep and ram, respectively. In these experiments, interestingly dose and duration of the pyrethroid was the same; however, in female animals ALT/AST increased, while decreased in male animals, which may be attributed to the influence of some of the male or female hormone(s) on the leakage of these enzymes. El-Tawil and Abdel-Rahman (1997) found that ALT from hepatocytes of female rat (cultured by collagenase perfusion harvesting technique) was significantly increased at 60 min of incubation with the 200 ng dose; whereas, 2 h of incubation was required for ALT from the same cells of male rats. Shah and Gupta (1997) found no biochemical changes at lower doses (24-60 $mg.kg^{-1}$ b. wt. per day) of permethrin; however, at higher doses (80-120 $mg.kg^{-1}$ b. wt. per day), an increase in ALT and AST levels was observed. El-Demerdash *et al*. (2003) reported that the activities of AST and ALT in liver and testes of rabbits were increased; contrarily, the activities of AST and ALT in plasma were decreased due to CY administration. Khan *et al*. (2009) reported increased serum concentrations of ALT on days 15 to 30 and those of AST on days 15 to 45 of the experiment.

Lactate dehydrogenase (LDH) was reported to be increased in various animals treated with CY (Shakoori *et al*., 1988; Das & Mukherjee, 2003; Manna *et al*., 2004a, b). Alkaline phosphatase (ALP) in various animals treated with CY was reported to be either increased (Anonymous, 1989; Manna *et al*., 2004b; Yousef *et al*., 2006) or decreased (Yousef *et al*., 1998; El-Demerdash *et al*., 2003). Few reports about no effect of pyrethroids on alkaline phosphatase are also available (Srivastava *et al*., 2005; Khan *et al*., 2009).

Increases of blood ALT, AST and LDH activities are related to liver damage and change in hepatic function (Manna *et al*., 2003). Increase of these enzymes has been attributed to the leakage of these enzymes to the blood stream (Yousef *et al*., 2006). The hepatic injury might be attributed to oxidative damage by free radicals (Manna *et al*., 2003; Muthuviveganandavel *et al*., 2008). Pesticide/insecticide-induced cellular changes diverge from mild escalation of metabolism to cell death. Elevation or suppression of enzymic bustle is associated with the intensity of cellular injury. Increased transaminase along with the decreased free radical scavengers are possibly the results of pathological alterations of α-CY taking place in liver. Increased activity of LDH may specify a shift towards anaerobiosis resulting in boosted production of lactic acid (Manna *et al*., 2003, 2004b). ALP is membrane bound enzyme, it is found on all cell membranes where active transport occurs and is hydrolase and transphosphorylase in function. The highest concentrations of ALP are found in the liver, biliary tract epithelium, bone and intestinal mucosa (Ravel, 1995). Serum ALP activity increases in case of damage to hepatic cells and obstruction of bile duct through proliferation of hepatic cells (El-Demerdash *et al*., 2003). Its decreased activity is taken as an index of parenchymal damage (Anwar, 2003).

Changes in creatinine and urea: Urea and creatinine increased with the treatment of pyrethroids (Table IV). Explanation for this could be that a metabolic product of creatine phosphate dephosphorylation in muscle is creatinine. Excretion occurs through a combination of glomerular filtration (70 to 80%) and tubular secretion (Ravel, 1995; Ahmad *et al*., 2011). The increase in the levels of serum creatinine may, therefore, be due to a combination of these two factors. Urea is a nitrogenous waste product. Deamination of amino acids in the liver leads to formation of urea at the end. It is transported in the blood to the kidneys where it is excreted in the urine. In rabbits, dietary protein concentrations and quality, withholding food

and natural diurnal rhythms can all affect urea concentrations. Higher levels occur in the late evening (Harcourt-Brown, 2002). The urea metabolism is further complicated by urea utilization by cecal microflora in rabbits, during catabolism or during periods of dietary excess. The rabbit has a limited capacity to concentrate urea and a greater volume of urine is required when urea load increases. Blood urea values may rise as a result of intense nitrogen catabolism during weight loss in rabbits. Similarly some parasites causing anemia in rabbits have been reported to have very high urea and creatinine values (Harcourt-Brown, 2002). Some workers (Yousef *et al*., 2003, 2006; Ahmad *et al*., 2011) reported increased urea and creatinine concentration in blood of pyrethroid treated animals, but opposing results have also been encountered (Table IV). Yousef *et al*. (2006) opined that increase in plasma creatinine and urea was due to their low clearance values. Low clearance values for creatinine and urea indicated diminished ability of the kidneys to filter these waste products from the blood and excrete them in the urine. As clearance levels were decreased, blood levels of creatinine and urea nitrogen increased.

CONCLUSION

It is concluded that pyrethroid group of insecticide may cause hematological and biochemical disturbances and damage to the tissues like that of kidney and liver. Therefore, claims of its being lesser toxic to the untargeted animals may be true in limits of doses used. Application of pyrethroids may, therefore, be carried out on recommended doses, and cautions related to other insecticides must be exercised for this group of insecticides as well.

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