Subchronic Toxicity Of α-Cypermethrin In Male Rat

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ABSTRACT

The aim of the present study was to investigate the possible toxic effects, exerted by the pyrethroid α-cypermethrin (α-CP) on rat testes in a subchronic experiment. Male Sprague-Dawley rats were treated per os every other day for 9 weeks with 5.54, 11.08, or 22.16 mg/kg α-CP (1/100, 1/50, 1/25 LD_{50}). On the day following the last treatment, the animals were sacrificed. Activities of various testes enzymes, serum testosterone level, testes antioxidant status, and semen picture and testes pathological changes were studied. Results revealed that α-CP increased the testes levels of alkaline phosphatase (ALP) and gamma glutamyl transaminase (GGT) activities, while decreased the alanine transaminase (ALT) activity. Serum testosterone level was significantly decreased. Malondialdehyde (MDA) level was increased following different doses of α-CP administration. A significant decrease in Epididymal sperm cell count, live sperm percentage and motility percent and a significant elevation in the number of abnormal shape of sperm were noticed in all treated groups as compared to control. Histopathplogical changes in the form of increase in seminiferous tubule diameter and disruption of the seminiferous epithelium with vacuolization and sloughing were recorded. The effect of α-CP was dose-dependent. These results clearly demonstrate the adverse effects of α-CP pesticide on fertility and reproduction in male rats.

INTRODUCTION

Synthetic pyrethroids are used to protect crops, animals, and humans from a wide range of insects *(1)*. In the last few years, it has increased several-fold in the application of these compounds due to their low mammalian toxicity and limited persistence in soil as compared to organochlorine insecticides *(2)*. However, these compounds are highly toxic to fish and other lower aquatic organisms *(3)*, and their widespread use has led to toxic effects in plants, animals and human beings.

Cypermethrin is the most widely used Type II pyrethroid pesticide. It is a composite synthetic pyrethroid, a broad spectrum, biodegradable insecticide, and a fast-acting neurotoxin with good contact and stomach action. It is used to control large scale of pests, including moths, pests of cotton, fruit, and vegetable crops. Consistent with its lipophilic nature, cypermethrin has been found to accumulate in body fat, skin, liver, kidneys, adrenal glands, ovaries, testes and brain *(4)*.

The acute toxicity of pyrethroids is mostly lower than other groups of insecticides and do not influence cholinesterase function *(5)*. The acute oral LD_{50} of α-CP in male rats is 554 mg/kg *(6)*.

Cypermethrin induced a significant reduction in male rat fertility at dose level of 39.66 mg per day for 90 day, as the number of females impregnated by them was significantly reduced; the number of implantation sites and the number of viable feti were significantly reduced in females mated with males. Epididymal and testicular sperm counts as well as daily sperm production were significantly decreased in exposed those males. The serum levels of testosterone, follicle-stimulating hormone and luteinizing hormone were significantly reduced. A significant decrease in the perimeter and number of cell layers of the seminiferous tubules. The testes were infiltrated with congested blood vessels with marked hemorrhage and a significant accumulation of connective tissue surrounding the seminiferous tubules, which contained a large number of immature spermatids *(7)*.

Male rabbits given sublethal dose (24 mg/kg b. wt. every other day for 12 weeks) of cypermethrin showed significant decreases in ejaculate volume, sperm motility (%), and total

motile sperm per ejaculate, packed sperm volume and semen initial fructose. On the other hand, it increased the numbers of abnormal and dead sperms, and initial hydrogen ion concentration *(8)*. A significant elevation in the number of abnormal sperm head shape was noticed in mice administered ip. with a suspension solution of cypermethrin at the doses of 30 mg, 60 mg and 90 mg/kg b. wt. daily for 5 days *(9)*.

Single oral LD_{50} of α-CP increased the malondialdehyde (MDA) level and decreased the activities of catalase (CAT), superoxide dismutase (SOD) and glycogen in rat liver. It also increased the serum aminotransaminases (AST, ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities, in addition to blood glucose level, plus producing some cytotoxic effects in liver as congestion, hemorrhage and necrosis *(10)*.

This research was aimed to study serum testosterone level, semen picture and testis histopathology in addition to estimation of lipid peroxidation and ALT, ALP, GGT enzyme activities in rat testes after α-CP administration.

MATERIAL AND METHODS

Chemicals

FAS TAC® (Alpha cypermethrin, 5%E.C.): alfacyano-3-phenoxybenzyl-1 RScis-Trans-3-(2, 2-dichlorovinyl) 2,2dimethyl-cyclopropane carboxylate, IUPAC) produced by CYANAMID Company. All chemicals used in this study were of analytical grade.

Kits

Testosterone kits were purchased from Biozyme® company.

Malondialdehyde kits were purchased from *Biodiagnostic*® company.

ALT, ALP and GGT kits were purchased from Diamond® company.

Experimental animals

Forty mature healthy male Sprague-Dawley rats weighing 150-200 g (purchased from Animal House Colony, Giza, Egypt) were housed in stainless-steel cages with hard wood shavings as bedding. Animals were accommodated to the laboratory conditions for one-week before experiment. They were maintained on balanced ration and given water *ad-libitum* throughout the experimental period (9 weeks).

Experimental design

Four groups (10 rats each) were treated per os by gavage, with α-CP, twice weekly for 63 days to cover a complete spermatogenic cycle in the following manner:

Group 1 untreated control
Group 2 α-CP 5.54 mg/kg (1/100 LD_{50})
Group 3 α-CP 11.08 mg/kg (1/50 LD_{50})
Group 4 α-CP 22.16 mg/kg (1/25 LD_{50})

At the end of the experimental period (64^{th} day), all animals were anaesthetized employing anesthetic ether. Blood samples were collected from each animal via the retro-orbital venous plexus after fasting for 12 h., left to clot then centrifuged at 5,000 rpm for 10 min to separate serum in order to determine testosterone level by the immuno-enzymatic method (IEMA) according to the instruction of the kit (Biozyme Co., Switzerland). Testes were surgically removed from the anesthetized rats. One testis washed in ice cold 1.15% KCl and was then taken for homogenization in a Teflon glass homogenizer while maintaining the unit in ice bath. The homogenate was centrifuged at 10,000 rpm for 20 min; the supernatant was collected and used for measuring lipid peroxidation *(11)* and ALT*(12)*, ALP *(13)*, GGT *(14)* enzyme activities. The other testis was fixed in 10% neutral buffered formalin. Sections of 3-5µm thickness were stained with hematoxylin and eosin for histological examination *(15)*. The Epididymal contents were collected to investigate the sperm cell concentration, live and dead sperms, sperm motility and the incidence of abnormal sperms *(16)*.

Statistical analysis

Student's t-test (unpaired, two-tailed) was used for statistical analysis *(17)*.

RESULTS

Clinical signs

There was no mortality between rats in all groups. Minor symptoms of neurotoxicity, such as abnormal gait and nervousness, were noticed in a small number of animals (4/10)

treated with 1/100 LD_{50} of α-CP. Such symptoms were more clear between rats treated with 1/50 LD_{50} α-CP (9/10). Group treated with 1/25 LD_{50} of α-CP showing, typical signs of cypermethrin toxicity in the form of salivation, hunched back, splayed gait, scratching, ataxia, convulsions and hypersensitivity, which usually commenced 1.5–2 h after dosing.

Semen pictures

A significant decrease in Epididymal sperm cell count, live sperm percentage and motility percent in addition to a significant elevation in the number of abnormal shape of sperm were noticed in all treated groups as compared to control. It was observed that the adverse effect of α-CP on semen picture was dose-dependent, (Table-1); (Figs. 1, 2, 3 and 4).

Table 1. Effect of oral administration of alpha cypermethrin (twice weekly for 9 weeks) on semen picture of male rats (n=10). Data are represented as mean ± SD.

Parameter	Control	1/100 LD_{50}	1/50 LD_{50}	1/25 LD_{50}
Sperm cell conc. X 10^6	57.12±1.4	$52.3±1.12^a$	$49.1±1.32^b$	$43.5±1.16^c$
Live sperms %	90.13±1.23	$86.32±1.41^a$	$81.27±1.36^b$	$73.25±1.0^c$
Motility %	89.42± 1.24	$77.21±1.27^a$	$70.21±1.13^b$	$59.14±1.0^c$
Abnormality %	5.75 ± 0.7	$8.1±1.2^a$	$10.41±1.4^b$	$13.0±1.73^c$

N.B: Values in the same row with different superscripts vary significantly at $p < 0.05$.

Biochemical profile

Treatment of rats with α-CP caused changes in the levels of MDA, ALT, ALP and GGT in the rat testis compared to control (Table-2). MDA level was increased following different doses of α-CP administration. Significantly diminished ALT activity was detected. Higher levels of ALP and GGT activities were recorded corresponding to the dose of α-CP used. The serum level of testosterone was significantly reduced in males exposed to all doses (Table-2). The effect of α-CP on these biochemical parameters was dose-dependent.

Table 2. Effect of oral administration of alpha cypermethrin (twice weekly for 9 weeks) on some biochemical parameters of male rats (n=10). Data are represented as mean ± SD.

Tissue	Parameter	Control	1/100 LD_{50}	1/50 LD_{50}	1/25 LD_{50}
Serum	Testosterone(nmol/L)	7.32±0.3	$6.73±0.21^a$	$6.16±0.13^b$	$5.12±0.32^c$
Testes	MDA (nmol/mg ptn)	2.3±0.1	$2.7±0.12^a$	$3.3±0.1^b$	$4.3±0.2^c$
	ALP (IU/l).	210.2± 2.0	$227± 2.4^a$	$241±2.6^b$	$273±3.1^c$
	ALT (IU/l).	295.2 ± 0.8	$278±0.7^a$	$258±0.84^b$	$235±0.81^c$
	GGT (IU/l).	3517 ± 4.3	$3619±4.4^a$	$3674±5.2^b$	$3727±4.6^c$

N.B: Values in the same row with different superscripts vary significantly at $p < 0.05$.

Histopathologic changes

Histopathology was conducted to characterize the manifestations of testicular injury induced by α-CP. Rats received α-CP at dose level of 22.16 mg/kg showed an obvious increase in seminiferous tubule diameter and disruption of the seminiferous epithelium with vacuolization and sloughing (Fig. 5). The seminiferous tubule terminal segments, the rete, and the efferent ducts contained large amounts of sloughed seminiferous epithelial debris (Fig. 6). The degree of testicular damage was less obvious in rats received α-CP at dose level of 5.54 and 11.08 mg/kg respectively when compared to that received 22.16 mg/kg.

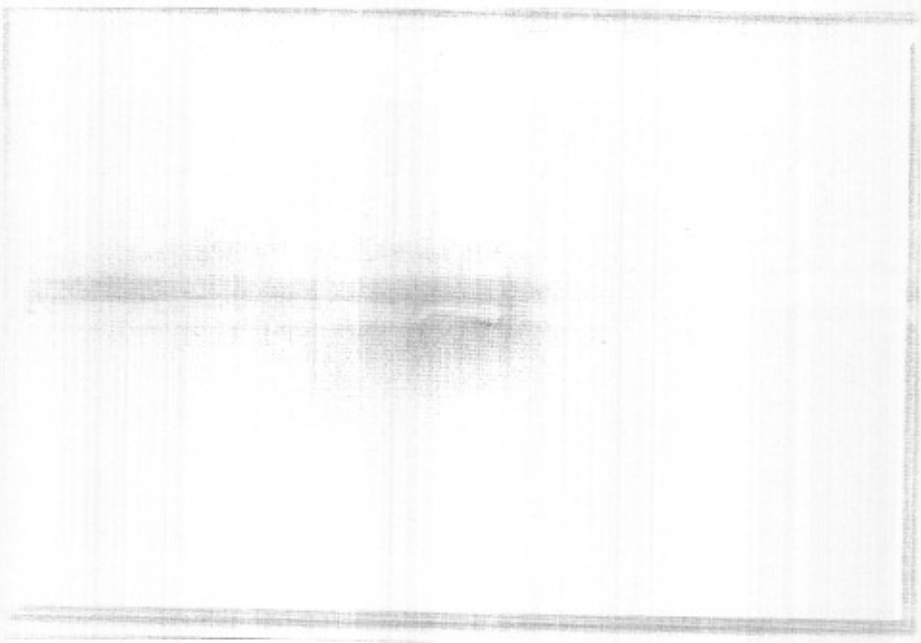

Fig. 1. A photograph of rat spermatozoa from albino rat administered orally alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing sperm abnormalities in the form of bent head sperm.

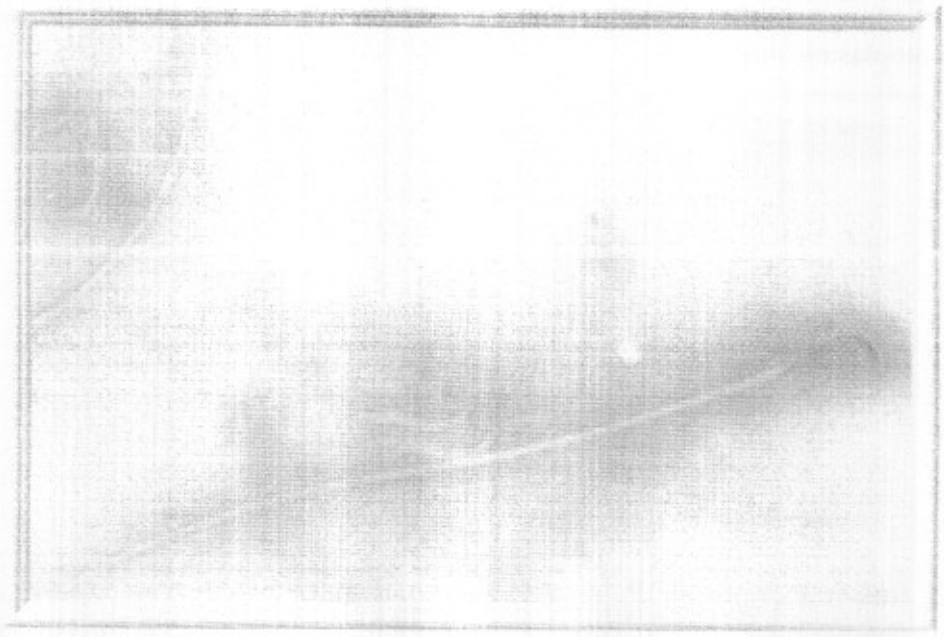

Fig. 2. A photograph of rat spermatozoa from albino rat administered orally with alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing sperm abnormalities in the form of detached head sperm.

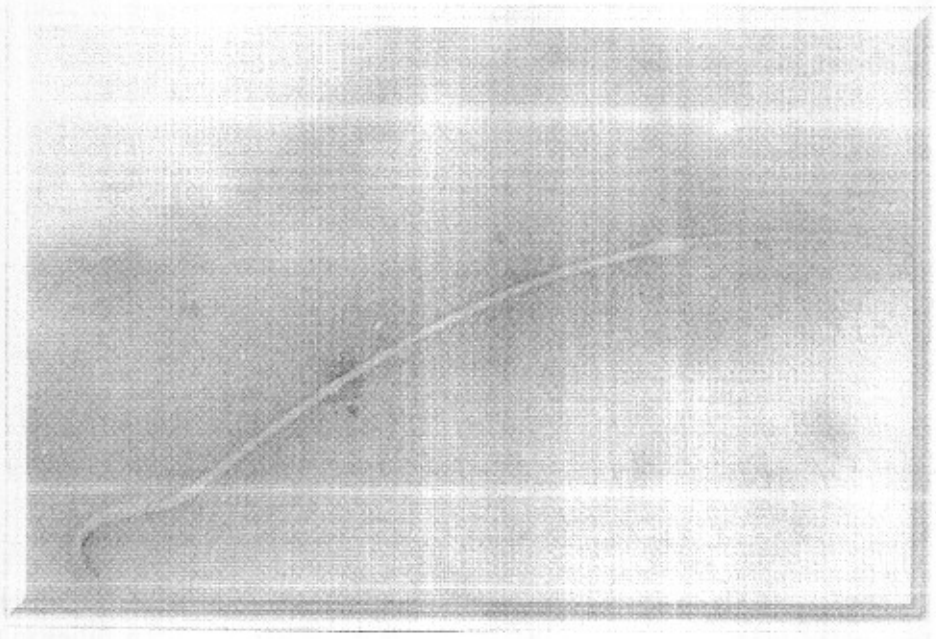

Fig. 3. A photograph of rat spermatozoa from albino rat administered orally alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing sperm abnormalities in the form of protoplasmic droplet.

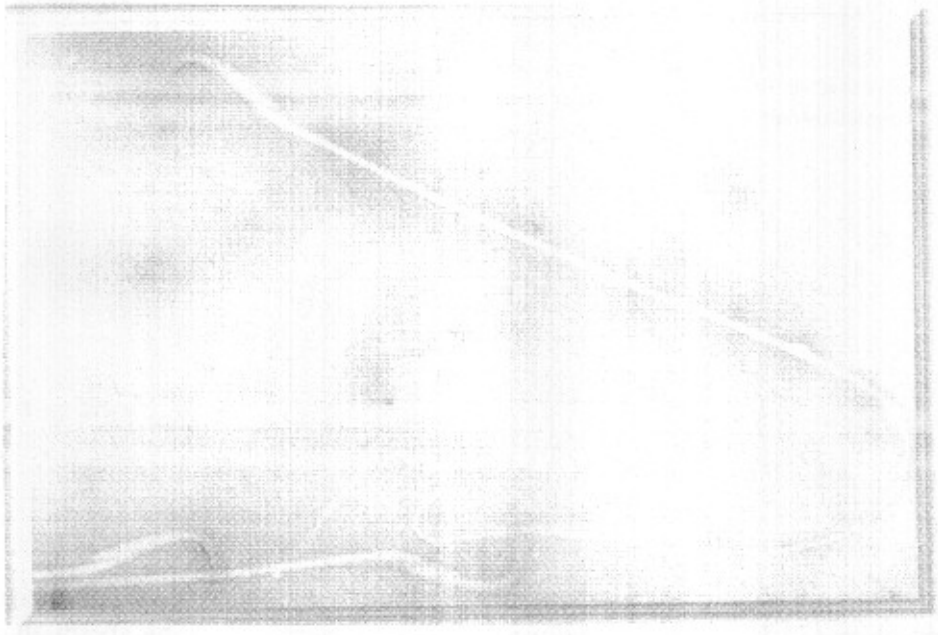

Fig. 4. A photograph of rat spermatozoa from albino rat administered orally alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing sperm abnormalities in the form of bent tail sperm with protoplasmic droplet.

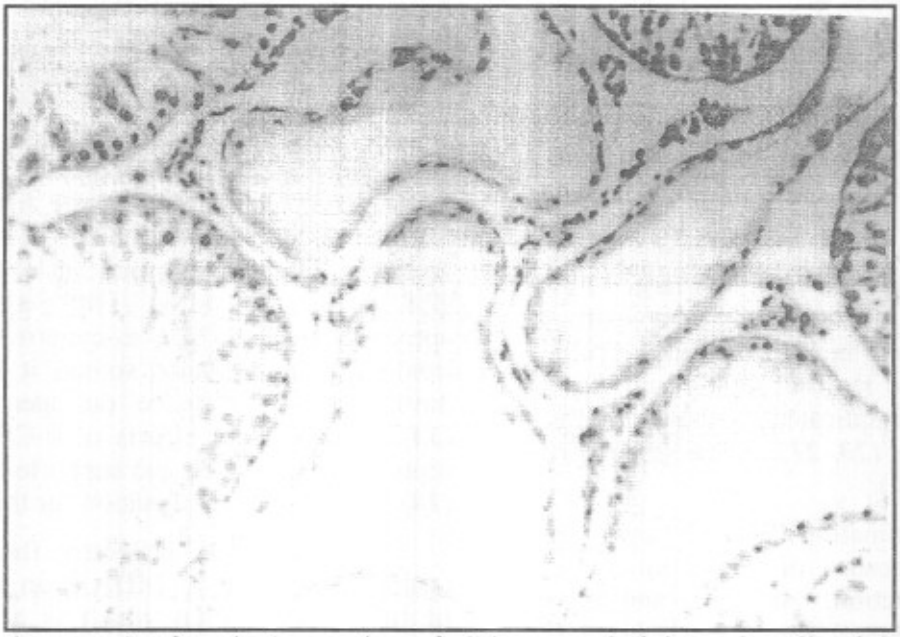

Fig. 5. A photograph of testicular section of albino rat administered orally alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing obvious increase in seminiferous tubule diameter and disruption of the seminiferous epithelium with sloughing (H & E X 1200).

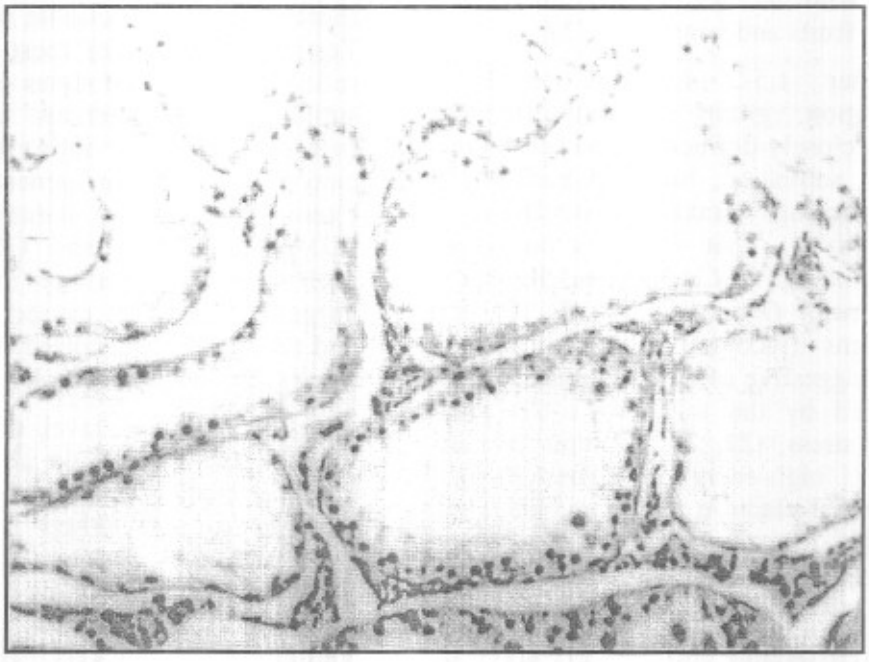

Fig. 6. A photograph of testicular section of albino rat administered orally alpha cypermethrin (22.16 mg/kg.) twice weekly for nine weeks, showing the seminiferous tubule terminal segments, the rete, and the efferent ducts contained large amounts of sloughed seminiferous epithelial debris (H & E X 1200).

DISCUSSION

Pyrethroids are highly toxic to insects and have been widely used in the past few years in agriculture. Synthetic pyrethroid used preferentially in place of organophosphates and organochlorines since they are highly effective for a wide range of insects, exhibit low toxicity to mammals and birds, and undergo rapid biodegradability *(18, 19)*. Several studies reported that reactive oxygen species have implicated in the toxicology of organochlorine *(20, 21)*, organophosphate and pyrethroids *(22)*.

Contamination through cypermethrin may occur because of unskilled application during production, storage, and, mainly, spraying of vegetables and fruits, such as potatoes, paprika, tomatoes, cherries, peaches and apples *(23)*. Through these, many people might become contaminated: first, those working with it and second, those eating pretreated fruits and vegetables *(24)*.

After 1.5-2 h from α-CP oral administration, group received 1/25 LD_{50} showed a closely defined sequence of toxicity signs like salivation, hunched back, splayed gait, scratching, ataxia, convulsions and hypersensitivity. That result is corroborated with the findings of ***Crofton*** **and Reitter and World** ***Health Organization*** *(25, 26)*. These motor signs (recorded in all groups) are strongly suggestive of CNS toxicity which can be clarified by the fact that α-CP produce oxidative stress, *(22, 27, 28)* that resulted in leakage of high-energy electrons along the mitochondrial electron transport chain, which causes the formation of superoxide anion radicals that has been speculated to be involved in neurodegenerative disorders *(29)*.

The overall results of this study showed that oral exposure to α-CP introduces significant oxidative stress in testicular tissue of rats as was evident by the a significant decrease in epididymal sperm cell count, live sperm percentage and motility percent in addition to a significant elevation in the number of abnormal shape of sperm which noticed in all treated groups as compared to control. This result is in agreement with that reported by several authors *(7-9)*. The attractive clues for these results were due to pyrethroids affect the blood-testis barrier *(30, 31)* which protects germ cells from harmful influences *(32)*, beside the suppression of the testosterone hormone produced by leydig cells *(7,8)* that resulted in a deficient spermatogenesis *(33)*. α--cypermethrin is a lipid soluble substance sothat, it is likely to have more interference on sperm function *(34)*. Degenerative effects of α-CP on testes, reported in this work and supported previously *(10)*, also give an explanation for this result.

MDA level reflected the oxidative status of the tissue as MDA is an end product of lipid peroxidation which is a process of polyunsaturated fatty acids oxidative degeneration that resulted in impaired membrane structure and function *(35)*. Enzyme activity levels of ALT, ALP and GGT represented the functional status of the tissue. Testicular content of these enzyme activities reflected the overall status of the animal when subjected to exogenous modulate such as toxins, infection or injury *(36)*. A change in enzyme activity in general related to the intensity of cellular damage. The increased MDA level; ALP and GGT activities and decreased ALT activity in testicular tissue suggests that α-CP caused testicular damage and that damage occurred probably through a free radical mechanism *(37- 39)*.

The serum level of testosterone was significantly reduced in all dose levels, in a dose dependent manner; this result has been very well established in various other experimental conditions *(7, 8, 42)*. The direct effect of α-CP on testis tissue may be the cause of this result as α-CP cause loss of Leydig cell steroidogenic capacity resulted in both inhibition of the Leydig cell and significant damage to the seminiferous epithelium, i.e., germ cell loss through sloughing and apoptosis *(4)*. Beside the fact that α-CP induce oxidative stress in the testis which have affected the structure and function of cell organelles that manifested by reduction in testosterone level, also histopathological changes reported in this

work and supported recent report *(10)* may be a cause of this result.

The qualitative changes in the testes were apparent in all groups, but more severe damage was seen in the 4th group that received α-CP at dose level of 22.16 mg/kg orally. The major defects were disruption of the seminiferous epithelium with vacuolization and sloughing, this result was previously reported *(41, 42)*. Since the oxidative stress-status induces cellular damage *(43)*, the alteration of enzyme activity is related to the intensity of cell damage *(37)*. It is suggested that a decrease in ALT activity with concomitant decrease in the activity of free radical scavengers may be representative of α-CP induced pathological changes in the testis *(44)*.

The increased use of α-CP increased the risk of environmental contamination and the ensuing intoxication of non-target organisms in different ecosystems.

Abbreviations

MDA: Malondialdehyde, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transaminase.

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الملخص العربي

سمية الالفا سيبرميثرين على ذكور الجرذان

يوسف ـ غادة

أجريت هذه الدراسة لمعرفة الأثر السمي تحت المزمن لمبيد ألفا سيبرميثرين في ذكور الجرذان. تم أعطاء ألفا سيبرميثرين لذكور الجرذان عن طريق الفم يوم بعد يوم لمدة ٩ أسابيع بالجرعات الآتية (٥,٥٤, ١١,٠٨, ٢٢,١٦ ملجم/كجم). في اليوم التالي لآخر جرعة ذبحت جميع الجرذان و تم قياس مستوي بعض الأنزيمات و المؤشرات الحيوية للأكسدة في الخصية و نسبة التستستيرون في مصل الدم بالأضافة إلي صورة السائل المنوي و التغيرات الباثولوجية في الخصية. أوضحت النتائج أن ألفا سيبرميثرين يزيد من مستوي ألكالين فوسفاتيز و جاما جلوتاميل ترانس أمينيز بينما يقلل مستوي ألانين ترانس أمينيز في نسيج الخصية. معدل التستستيرون انخفض في مصل الدم مع زيادة في نسبة المالونديالدهيد.كما وجد أن ألفا سيبرميثرين يؤدي ألي حدوث نقص في عدد الحيوانات المنوية و نسبة الحيوانات المنوية الحية و كذلك نسبة الحركة مع وجود زيادة في التشوهات.كما أوضحت الدراسة وجود أتساع في محيط النبيبات الخصوية و تغيرات تحطيمية في النسيج الطلائي لها. هذه النتائج توضح جليا التأثير السمي لألفا سيبرميثرين علي الخصوبة في ذكور الجرذان.