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Comparative Histopathological Evaluation of Permethrin, Pirimiphos Methyl and Bendiocarb Toxicities in Testes, Liver and kidney of rat.

Afaf L. Nessiem; Nahed S. bassily and Salwa A. Metwally
National Organization for Drug Control and Research NODCAR, Egypt

Abstract

The increasing use of insecticides in agriculture and in public health calls for greater attention for studying their possible toxic effect (s) on man and animals. Acute toxic effects have been relatively well known whereas chronic effects require further studies. The aim of the present work was, therefore, to study the histopathological changes in testes, liver and kidney of rats due to 30 days feeding on diet containing permethrin, pirimiphos methyl and bendiocarb. The dose used for each insecticide represented a concentration that equals ten times the acceptable human daily intake. These doses are far below the LD50, but represent possible exposure doses. Forty male Sprague- Dawley rats were divided into 4 equal groups. Animals of each group were fed either by normal diet, or diet mixed with permethrin (21.739 ppm), pirimiphos methyl (4.350 ppm) or bendiocarb (2ppm) for 30 days. Histological sections of testes, liver and kidneys were examined and histopathological changes and quantitative estimates were recorded. Incidence of spermatogenic suppression, Leydig cell atrophy and vacuolation of Sertoli cells were most prominent in testicular sections from primiphos methyl treated animal testis than in animals of the other groups. Peremethrin feeding resulted in the least deteriorative changes. In sections of liver, dilatation and congestion of blood sinusoids was most evident in the group treated with primiphos methyl and to less extent in those treated with bendiocarb. Swollen hepatocytes with pyknotic nuclei and incidence of apoptosis were also recorded. In kidney sections, vacuolar degeneration, tubular and capsular dilatation, and glomerular congestion were observed especially in primiphos methyl treated rats.

In conclusion, the obtained changes were of different severity as a response of exposure to permethrin, pirimiphos methyl or bendiocarb at the same equivelant of human acceptable daily intake.

Introduction

The use of pesticides has been largely expanded during the last fifty years. More than 3 million tons of approximately 600 different chemicals are applied annually throughout the world. The WHO (1992), reported that 3 million pesticide poisoning cases occurred annually and resulted in 220 000 deaths allover the world. In the developing countries the situation is worse, since higher proportions of pesticidepoisoning and deaths occurred, the reasons behind this include inadeq - uate occupational safety standards and insufficient knowledge of pesticide hazards. Some pesticides are carcinog - enic, most are teratogenic, and others are mutagenic. All are attributed to normal agriculture use (US Geological survey 1997). So, it is safe to assume that sooner or later higher percentages of our people (especially in developing

Refree : Prof ; *Dr.* Fathey Matter .

countries) will suffer from some serious forms of diseases like cancer and kidney failure (Cheraskin 2000).These diseases will result from toxins in air we breathe, food we eat and water we drink.

Among the potent synthetic insecticides that have been increasingly employed in recent years are synthetic pyrethroids, organophosphates and car - bamates. Pyrethroids administration resulted in deleterious effects on liver and blood parameters, and to induce chromosomal aberrations (Ishmael and Lithfield, 1988 and Institoris *et al*., 1999a and b), to suppress erythropiosis and hemoglobin synthesis and to increase the number of leukocytes (Tos-Luty *et al*., 2001). Pyrethroids were also reported to cause slight activation of cytochrom P 450 1A and 2B- mediated reactions (Kostka *et al*., 1997 and Moresseau *et al*. 1999) and to act as a tumor promotor at a non-hepatotoxic doses (Hemming *et al*., 1993). They may inhibit the G2 phase in the cell cycle and consequently may suppress the cell entering into the stage of mitosis (Kostka *et al*., 2000). Pyrethroids were also found to affect male and female reproductive system (Eil and Nisuls, 1990).

Organophosphate insecticides were in existence since 1854, but were not recognized as having toxic potentials until 1930 (Marrs, 1993). These compounds induce significant fall of body weight (Gajewski and katkiewuz, 1981), and reduce glycogen content in liver and kidney (Awasthi *et al.*, 1984). Pirimiphos methyl is known to affect the proteolytic enzyme activities in rat heart, kidney, brain and liver (Mantle *et al.*, 1997). It induces significant inhibition of brain and erythrocyte-acetyl cholinesterase, plas - ma pseudo cholinesterase and non-specific carboxyl esterase of brain, plasma and kidney (Rajini *et al*.,1989).

Carbamates may represent a class of chemicals which function through a mechanism separate from ligand-receptor binding, as they may act as general endocrine modulators in mammalian cells (Klotz *et al*., 1997). They induce dose dependent decrease in body weight (Pant *et al*., 1995a and b and Kackar *et al*., 1997) and significant change in the weight of testes, epididymides and accessory sex organs (Pant *et al.*, 1995b). Carbamate insecticides were found to inhibit both aggregation and arachidonic acid metabolism in human blood platelets (Krug *et al*., 1988), to inhibit brain and blood acetylcholinesterase, liver glucose 6 phosphatase and succinic dehyd - rogenase (Fayez and Kilgore 1992).

The wide spread use of the abovementioned insecticides in agricu - lture and in public health drew our attention for studying their possible toxic action (s) in man and animals. The aim of the present work is to study the histopathological changes in liver, kidney and testes due to daily oral feeding for 30 days by diet containing permethrin, pirimiphos methyl and bendiocarb, each at a concentration that equals ten times the acceptable daily intake (a concentration that may represent the real life situation regarding exposure to the tested compounds).

Material and Methods

Animals:

male Sprague-Dawley rats of 110-120 gm body weight were obtained from the breading colony of the National Organization for Drug Control and Research (NODCAR), Cairo. They were housed as 7 animals per cage.

Insecticides:

Permethrin represents pyrethroid insecticides. Pirimiphos methyl repre-sents organophosphorus insecticides.

Bendiocarb represents carbamate insecticides.

Experimental design:

rats were divided into 4 equal groups (each consisted of 10 animals):

Control group: animals were fed norm - al diet and served as a control.

Permethrin group: animals were fed diet containing 10 times the human maximal acceptable daily intake of permethrin (21.739 ppm) for 30 days.

Pirimiphos methyl group: animals were fed diet containing 10 times the human maximal acceptable daily intake of pirimiphos methyl (4.350 ppm) for 30 days.

Bendiocarb group: animals were fed diet containing 10 times the human maximal acceptable daily intake of bendiocarb (2 ppm) for 30 days.

Histological manipulation:

Twenty- four hours after the last day of feeding with insecticides, animals of each group were killed by narcosis. Testes, liver and kidneys were removed, fixed in buffered formol and prepared for paraffin sectioning. Six micron sections were mounted on clean slides, and stained by hematoxylin and eosin (Culling, 1974).

Quantitative analysis:

Low magnification ten sections from the testis were used to count the number of seminiferous tubular sections that do not contain all the spermatogenic components including spermatozoa in their lumen. Such sections were considered as having suppressed spermatogenesis. High magnification sections were used to count Sertoli cells with vacuolar degeneration and Leydig cells that lack the normal healthy appearance.

Liver sections were used to count the percentage of hepatocytes with vacuolar degeneration and those with apoptotic morphology.

Results

The testis

Sections from the testes of the different groups are represented in plates (1,2.).

The sectioned seminiferous tubules in control animal testis are closely packed with regularly distributed interstitial tissues (plate 1). Different stages of spermatogenesis are represented in the arrangement and number of layers in the tubule. Spermatozoa are clearly visible in the tubular lumen (plate 2).

Sections in the seminiferous tubules of permethrin-treated animal testis show almost normal arrangement of spermatogenic cells (plate 1). The Sertoli cells, however, are vacuolated. Fewer spermatozoa are found in the lumen compared with control. The interstitial matrix is swelled with aggregation of Leydig cells (plate 2).

The seminiferous tubules of pirimiphos methyl treated rat testis are smaller in diameter with irregular shape and depressed spermatogenesis(plate 1). The Sertoli cells are highly vacuolated. The layers representing spermatogenic cells are highly disturbed. Giant cells are clearly represented in the lumen of the tubules. There is a near complete absence of spermatozoa (plate 2).

The contours of sections of seminiferous tubules from the testes of bendiocarb fed rats appear also irregular and widely separated. Signs of swelling can also be noticed in the interstitial area. (plate 1). In some sections, the spermatozoa appear in the middle of the lumen without clearly differentiated tails (plate 2).

Table (1): Incidence of histological changes in testicular tissue of rats fed diet containing permethrin (21.739 ppm), pirimiphos methyl (4.35 ppm) or bendiocarb (2 ppm)

Treatment	Incidence (%)					
	spermatogensis		leydig cell atrophy		vacuolar degeneration of sertoli`s cells	
	normal	supressed	present	absent	present	absent
normal diet	100%	0%	0%	100%	0%	100%
permethrin containing diet	80%	20% *	0%	100%	10%	90%
Pirimiphos methyl containing diet	10%	90% ***	90% ***	10%	90% ***	10%
bendiocarb containing diet	60%	40% **	40% **	60%	30% **	70%

*, **, *** statistical difference at p<0.05, <0.01 and < 0.005, respectively compared with the control. Statistical analysis using chi-square test.

Table (1) represents the incidence of the histological changes that occurred in rat testes due to daily oral feeding by diet containing permethrin, pirimiphos methyl or bendiocarb. The data showed that spermatogenesis was suppressed in 20, 90 and 40% in sections of seminiferous tubules in the testes of animals fed by diet containing permethrin, pirimiphos methyl or bendiocarb, respectively. Leydig cell atrophy was encountered in 90% and 40% of animals treated with pirimiphos methyl or bendiocarb, respectively. The obtained data showed also that vacuolar degene-ration in Sertoli cells was present in 10, 90 and 30% of animals due to daily oral feeding with permethrin, pirimiphos methyl or bendiocarb, containing diet, respectively.

The liver

Compared with control, sections in the liver of rats treated with permethrin revealed normal lobular architecture with mild changes in form. Scattered inflammatory cell aggregates and strands of fibrosis were observed in the portal area (plate3). There are scattered mildly dilated sinusoids with prominent Kupffer cells and intravascular leucocytes. The hepatocytes were mildly swollen and showed few scattered apoptotic cells. It also showed occasional hepatocytes with pyknotic nuclei and acidophilic cytoplasm together with few scattered binucleated hepatocytes (plate 4).

In pirimiphos methyl treated animals, the histolgical changes in liver tissue were severe. Portal areas were markedly expanded, showing dilated portal veins, areas of fibrosis and inflammatory cellular infiltrate It also showed areas with inflammatory cell aggregates. Signs of hemorrhage can also be seen (plate 3). Hepatocytes showed marked ballooning and vacuolization, together with marked sinusoidal dilatation and high incidence of apoptotic body formation . Moreover, binucleated hepatocytes could be also seen Sections in liver of the animals fed with diet containing bendiocarb showed diffuse and prominent cytoplasmic vacuolation, mildly dilated sinusoids and scattered apoptotic body formation (plate 4).

Table (2) : Incedence of histological changes in liver tissue of rats fed diet containing permethrin(21.739ppm), pirimiphos methyl (4.350ppm) and bendiocarb (2 ppm).

Treatment	Incidence (%) vacuolar degeneration				(a) Mean apoptotic index
	negative	mild	modrate	severe	
normal diet	100%	0	0	0	0
permethrin containing diet	90%	10%	0	0	8%
pirimiphos methyl containing diet	0	0	0%	100% ***	80%
bendiocarb containing diet	50%	0	50% **	0	40%

(a), apoptotic index = number of apoptotic cells in 1000 cells devided by 10
*, **, *** statistical difference at p<0.05, <0.01 and < 0.005, respectively compared with the control . values were analyzed using chi-square test.

Table (2) shows the incidence of vacuolar degeneration and the mean apoptotic index in liver tissue due to feeding with diet containing permethrin, pirimiphos methyl or bendiocarb. The data present in this table show that permethrin feeding induced mild vacuolar degeneration in 10% of hepatocytes, irimiphos methyl induced severe vacuolar degeneration in 100% of hepatocytes, while bendiocarb induced only moderate effect in 50%, of the hepatocyte population. Moreover, the table shows that the mean induced apoptotic indices were 8% in permethrin, 80% in pirimiphos methyl, and 40% in bediocarb fed animals.

The Kidney

Microscopic structure of kidney tissue of rats treated with permethrin was almost normal, with normal appearing tubular and glomerular structure, where as in rats fed on diet contains pirimiphos methyl (plate 5), the histological examination revealed vacuolar degenerative changes in epithelial cells lining some renal tubules. Glomerular tufts were seen showing hyper cellularity with evidence of congestion The lumen of Bowmans capsule was dilated.

Sections in the kidneys of rats subjected to bendiocarb treatment, showed widely dilated distal convoluted tubules. Necrotic changes were predominant in proximal convoluted tubules. The Bowmans capsule was dilated with some signs of congestion in the glomerular capillaries (Plate 5).

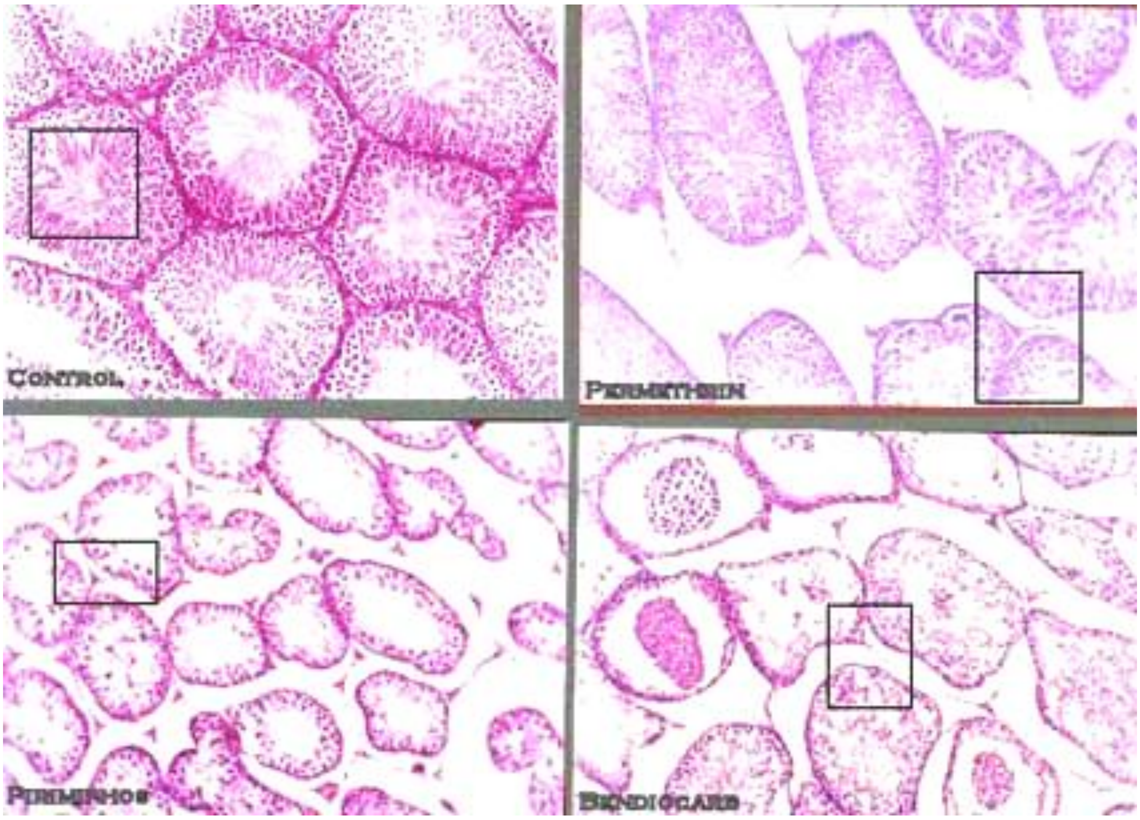


Plate (1): Sections in the testes of control and insecticide treated animals. In the control, the seminiferous tubules appear in the different phases of spermatogenesis, the lumen is loaded with mature spermatozoa and the interstitial area containing the Leydig cells is continuous. In Permethrin treated group, signs of spermatogenesis are less prominent,the interstitial area suggest signs of swelling. In perimiphos methyl treated group, the seminiferous tubules have smaller diameter and irregular in shape, most of the tubules have suppressed spermiogenesis and the interstitium is swelled. In bendiocarb treated group, there is moderate change in tubular diameter and shape irregularity with interstitial swelling. The areas in the squares are represented at higher power in plate 2 (Hx,E X200)

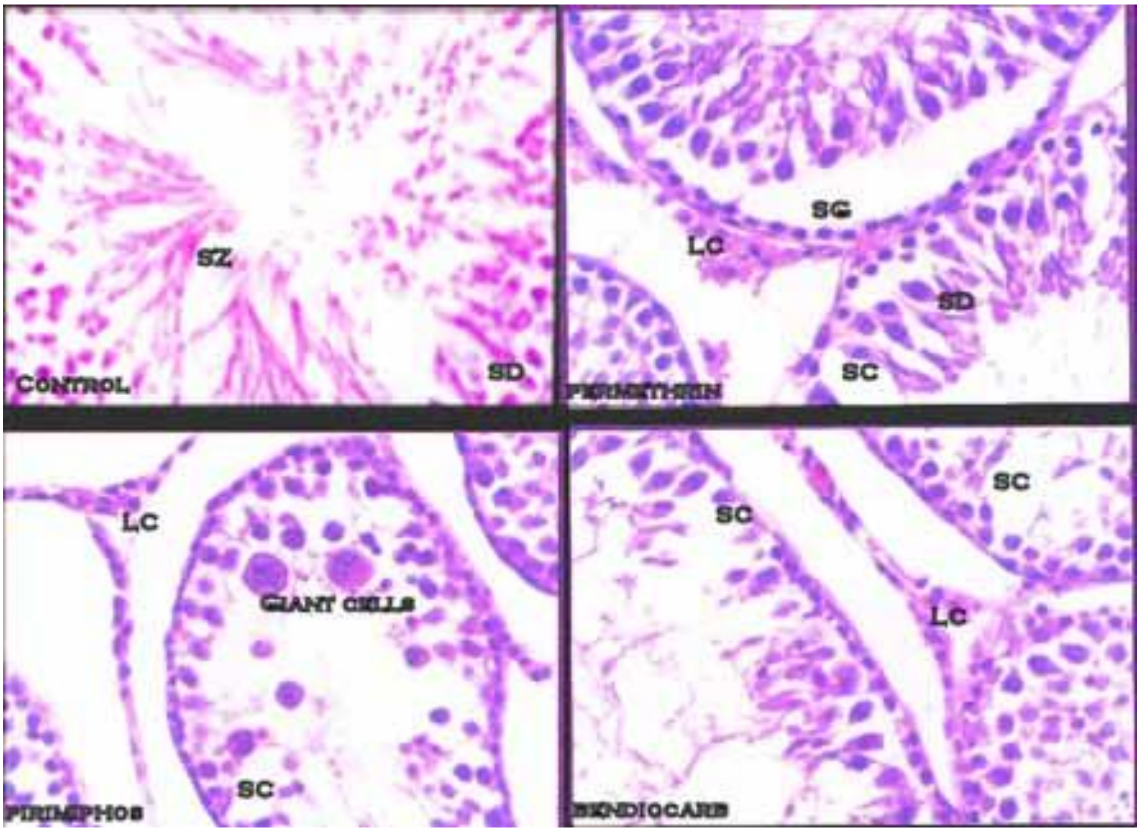
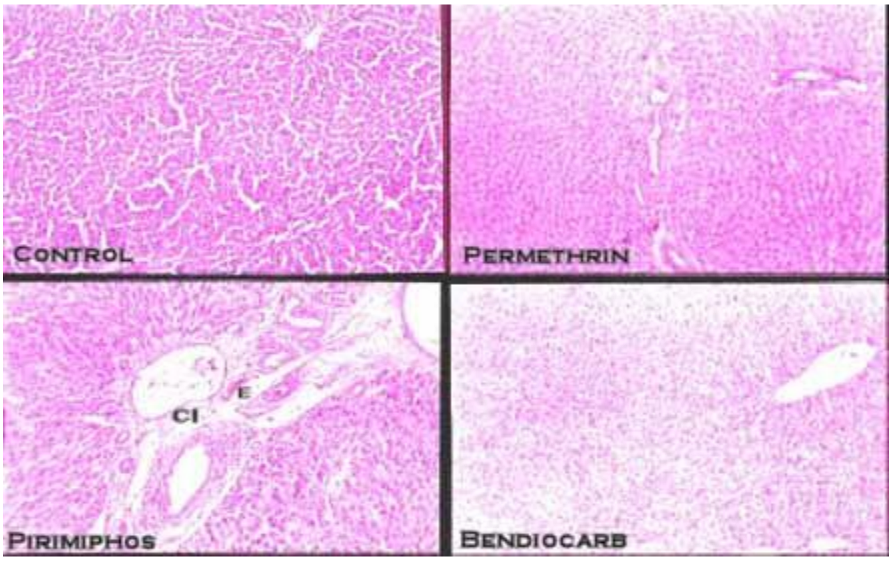


Plate (2): Sections in the testes of control and insecticide treated animals. In the control, the lumen of the seminiferous tubules appear loaded with mature spermatozoa (SZ) spermatids (SD) in different phases of normal differentiation. In Permethrin treated group, the spermatogonia (SG) form a continuous basal layer . The spermatids (SD) are more or less normal while Sertoli cells (SC) are moderately vacuolated. Leydig cells (LC) are aggregated near by the basement membrane with some swelling in the interstitium. In perimiphos methyl treated group, the seminiferous tubules have suppressed spermiogenesis with formation of giant cells. The Sertoli cells (SC) are highly vacuolated, the spermatogenic cell layer is not continuous and the Leydig cells(LC) are aggregated far from the basement membrane. The interstitium is highly swelled. In bendiocarb treated group, The Sertoli cell (SC) is also vacuolted, the spermatogenic cells are not well differentiated and the interstitial Leydig cells(LC) are aggregated far from the basement with interstitial swelling. (Hx,E X400



Plate(3): Sections in the liver of control and insecticide treated rats. The normal architecture in the control group is mildly disturbed in the liver of permethrin treated group. In primiphos methyl treated group, there is extravasated blood corpuscles (E) in the portal area. Portal areas were markedly expanded, showing dilated portal veins, areas of fibrosis and inflammatory cellular infiltrate (CI). Vacuolation of hepatocytes is illustrated in bendiocarb treated group. (Hx,E x40)

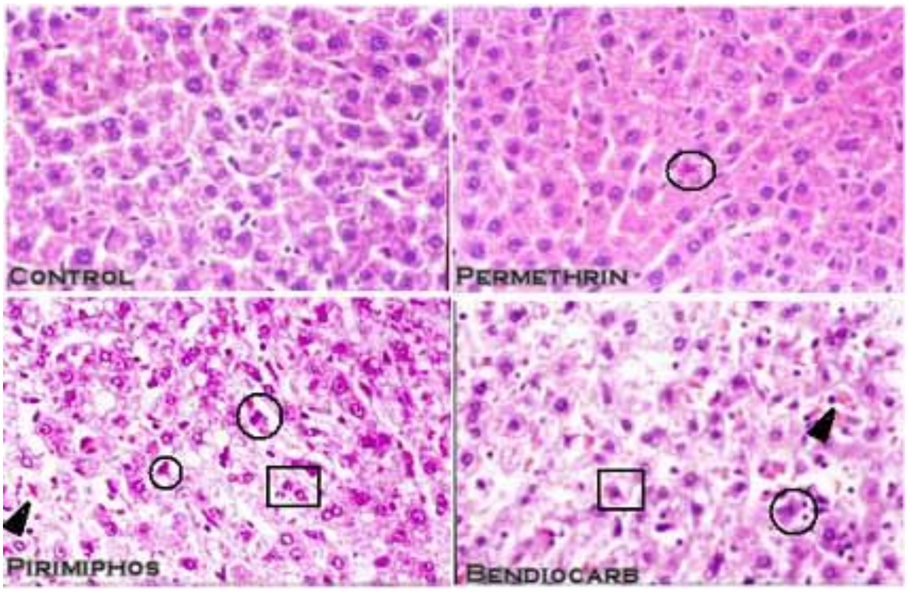


Plate (4): Histological sections of liver of control and treated animals. Compared with sections from control, sections in the liver of rats treated with permethrin reveal normal lobular architecture with mild changes in form and scattered mildly dilated sinusoids with prominent kupffer cells and intravascular leucocytes. The hepatocytes were mildly swollen and showed few scattered apoptotic cells (circle). It also showed occasional hepatocytes with pyknotic nuclei and acidophilic cytoplasm together with few scattered binucleated hepatocytes. In pirimiphos methyl treated animals hepatocytes showed marked ballooning and vacuolization (square), together with marked sinusoidal dilatation(arrow head) and high incidence of apoptotic body formation (circle). Sections in liver of the animals fed with diet containing bendiocarb showed diffuse and prominent cytoplasmic vacuolation (square), mildly dilated sinusoids (arrow head) and scattered apoptotic body formation (circle). (Hx, E X 400).

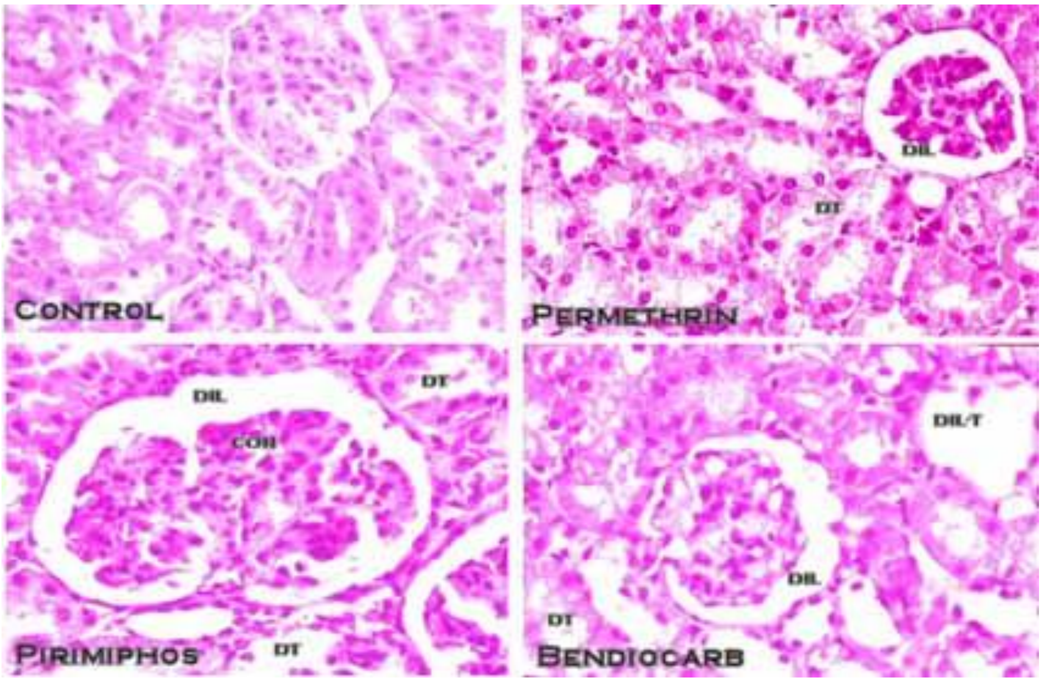


Plate (5): Microscopic structure of kidney tissue of rats treated with permethrin was almost normal, with mild capsular dilatation (DIL) and minor tubular cell degeneration (DT), where as in rats fed on diet containing pirimiphos methyl, there is vacuolar degenerative changes in epithelial cells lining some renal tubules (DT). Glomerular tufts were seen showing hyper cellularity with evidence of congestion (CON) and capsular dilatation (DIL). In the kidneys of rats subjected to bendiocarb treatment, there is widely dilated distal convoluted tubules (DILT). Necrotic changes were predominant in proximal convoluted tubules(DT). The Bowmans capsule was dilated (DIL) with some signs of congestion in the glomerular capillaries. (Hx, E X 400).

Discussion

Although insecticides represent one of the most widely encountered toxic pollutants, the need to its use in agriculture and house insect control is indispensable for the human life. Different groups of insecticides are used. The need for choosing the group with the least hazards to human life calls for active research towards this goal. In the present study, represen - tatives of three groups of insecticides were compared as to their effect on three vital organs in order to find out their differential hazard on these organs. The insecticides used represented one of natural origin, the pyrethroid permeth-rin, the organophosphate pirimiphos methyl and the carbamate bendiocarb. The organs were the testis, liver and kidney.

The histopathological changes obtained in the testicular tissue due to feeding diet containing permethrin indu-ced spermatogenic suppression, widen-ing between spermatogoia and Sertoli cell vacuolation,. Similar changes were also reported by Yenilmez (1995); Tyrkiel *et al*., (2001) and Abou-Donia *et al.*, (2003).

Abou-Donia *et al.* (2003) found that dermal daily application of perme - thrin (0.13mg/kg in ethanol) to human was implicated in the development of genitrourinary disorders among verter - ans of Persian Gulf War. On performing experiments on rats, these authors observed incidence of histopathological alterations in rat testes due to permethrin administration. The alterations included apoptosis of testicular germ, sertoli and leydig cells. In an earlier work, Yenilmez (1995), reported that permethrin oral administration induced widening between spermatogonia and sertoli`s cells, extrusion of the germ cells and increase in the number and size of the lipid inclusion in the leydig`s cell.

The obtained histopathological changes in testicular tissues were suggested to result from the binding of permethrin to the receptors of the androgen male sex hormone (Eil, *et al*. 1990) and/or binding to the benzodiazepine receptor that stimulates the production of male sex hormone testosterone (Ramadan *et al*., 1988). Another explanation was that the above mentioned histopathological changes may be due to the decrease in the blood testes barrier permeability (Abou-Donia *et al*.,2001). Daily feeding with diet containing pirimiphos methyl for 30 days was found to induce marked spermatogenesis suppression where primary and secondary spermatogonia were markedly reduced, reduced number of sperms and spermatids. The obtained changes included also interstitial leydig cell atrophy (incidence 100%), focal areas of widening between spermatogonia and Sertoli cell as well as scattered dilated vessels in different areas.

These changes were also reported in studies of Ray *et al*. (1988 and 1992); El Nahas *et al*. (1989); Debnath and Mandal, (2000)and Dutta and Meijer (2003). Ray *et al*. (1988) found impaired testicular functions due to detrimental changes in the seminiferous epithelium as the result of organophosphate insecticides. Massive degeneration of all varieties of germ cells, and remarkable reduction of the sperm counts were shown to result in response to organophosphates exposure (El Nahas *et al*., 1989 and Ray, *et al.*,1992). Debnath and Mandal, (2000) reported a reduction in the tubular diameter and testicular atrophy leading to degenerative changes in the germinal epithelium. More recently Dutta and meijer, (2003) showed that exposure to these insecticides resulted in testes disruption, enlarged sperm cells, the diameter of the seminiferous tubules were more widened and the number of viable spermatogonia being suppressed.

The obtained changes in the testicular tissue due to pirimiphos methyl may result from blocking the dihydrotesterone-dependent androgen receptors in a concentration dependent manner (Tamura, *et al.*, 2001).

The present work showed that daily oral feeding by diet containing bendiocarb result in histopathological changes in the rat’s testes. These changes include marked suppression of spermatogenesis (with 40% incidence), reduction in number of sperms, irregularity in shape and size of semineferous tubules. Moreover exfoliated clumps of degenerated spermatogenic cell and focal areas of separation were found. Pant *et al.* (1995a) reported that oral administration of 0.1, 0.2, 0.4, or 0.8 mg/kg. Carbamate insecticides induced significant decrease in the weight of epididymides, seminal vesicles, ventral prostate and coagulating glands as well as decrease in sperm motility and epididymal sperm count. The changes reported in the above- mentioned study included also Sertoli cell damage, germ cells alteration, accumulation of cellular depris and presence of giant cells in the lumen of seminiferous tubules (Pant *et al.*, 1995a). In another study (Kackar *et al.*, 1997), the authors reported that carbamate insecticides induced degeneration in seminiferous tubules and epididymal tubules, with sperm loss. According to Pant *et al*. (1995b), the obtained histopathological changes in the present work may be due to the decrease in the testicular enzyme sorbital dehydrogenase, to the increase in the lactate dehydrogenase which account to degeneration of the spermatogenic cell, and/or to the increase of gamma glutamyl transpeptidase and decrease of 6 phosphate dehydrogenase which was suggested to account for similar observed declines in epididymal sperm count, sperm motility and increased number of abnormal sperm.

In the present study, the exposure to oral daily feeding by diet containing permethrin was found to induce liver histopathological changes that include scattered midly dilated blood sinusoids with prominent kupffer cells, midly swollen hepatocytes and mild cytoplasmic vacuolation with few scattered apoptotic cells. Moreover, the changes were found to include hepatocytes with pyknotic nuclei and acidophilic cytoplasm, scattered binucleated hepatocyets as well as few mildy expanded portal areas, scattered inflammatory cell aggregates and strands of fibrosis. Ishmael and Lithfield, (1988), Kosta *et al.* (2000) and Tos-Luty, (2001) reported the effect of the insecticide on liver. Actually, Ishmael and Lithfield (1988), reported an increase in liver weight, liver atrophy, increase in the microsomal enzyme activity and proliferation of smooth endoplasmic reticulm due to 2500 ppm permethrin oral feeding to male mice. Also Kosta *et al.* (2000) showed that permethrin caused liver enlargement and an increase in binucleation in hepatocyets. Tos-Luty *et al*. (2001) revealed that oral administration of 5 and 25 mg/kg deltamethrin caused degenerative changes in the liver. Thus the obtained histopathological changes in the present work confirm that liver is a sensitive organ for permethrin toxicities (U.S.E PA, 1997). The observed changes may be explained on basis of the work of Gassner *et al.* (1997). These authors found that perme-thrin affects the energy coupling by mitochondria, where a concentration-dependent inhibition of glutamate and succinate sustained stat 3 respiration, a condition that causes disturbance in hepatic cell function and consequently hepatic histopathological changes.

According to the present findings, pirimiphos methyl induced severe changes in the liver tissues These changes include marked ballooning, vacuolation, marked sinusoidal dilation, and high incidence of apoptotic formation. In addition expanded portal areas, dilated portal veins, areas of fibrosis and inflammatory cellular infiltrate were also observed. Focal areas of hepatic necrosis with inflammatory cells aggregates, acidophillic cytoplasm and pyknotic nuclei were observed. Our Gajewski and Kathiewicz, (1981) found parenchymal cell atrophy due to i.p. injection with pirimiphos methyl. Other authors (Rajini and Krishnakumari, 1988), showed that dietary feeding at 10, 500, 1000 ppm for 28 days of pirimiphos methyl induced slight increase in the liver weight. According to the work of Kaminski *et al*.(1997), organophosphates were found to produce nonspecific effect on the morphology and enzymatic structure of the liver. On the other hand, Ito, *et al*.(1996) revealed that mixture of 20 organophosphate insecticides at 100 times the acceptable daily intake induced significant increase in the number and area of the preneoplastic lesion developed by diethylnitrosamine. On the other hand, unusual nonneoplastic lesions characterized by pericellular fibrosis, hepatocyte nuclear pleomorphism and intrasinusoidal foci of macrophages with intracellular crystalline structures were obtained as a result of oral feeding with diet containing 8000 or 16000 ppm of teterachlorovinophos (Ward, *et al.*, 1979).

The obtained changes in the structure of the liver, as a consequence of expo-sure to pirimiphos methyl may be due to the decrease in glycogen content of the liver tissue (Awasthi 1984), to the significant inhibition in esterases enzymes (Rajini, *et al.,* 1989) and/or to intracellular hypoxia in the liver tissue (Hettwer 1975). Also, the histological changes in the liver tissue due to pirimiphos methyl daily oral feeding may be explained to occur as a result of dysfunction of intracellular protein catabolic processes (Mantle *et al*., 1997) and / or due to the significant inhibition of activity of all of the cytoplasmic proteases responsible for the various stages of protein degradation cascade and essential for normal cell function (Mantle *et al*.,1997).

The hepatic histopathological changes induced by bendiocarb daily oral feeding include diffuse and prominent cytoplasmic vacuolation, mild dilated blood sinusoids and scattered apoptotic body formation. In his study, Hunter *et al*. (1978), reported vacuolated centrilobular hepatocytes. Moreover, Ram and Singh, (1988) showed cytoplasmolysis, nuclear pyknosis and necrosis, extensive degeneration of proliferated hepatocytes, dark stained debris of hepatomass due to the exposure of toleost fish to a safe dose of carbofuran (4.5 ppm).

Changes obtained in the liver tissue due to carbamate insecticides exposure, may be due to their effect on the liver ATPase activity, that may inhibit several biochemical function of phosphorylation of liver cells (El Tokhy and Girgis, 1983).

Histopathological examination of kidney tissue due to daily oral feeding by diet containing permethrin showed almost normal tissue with normal tubu - lar and glomerular structure. Reports of U.S. EPA, (1997) indicated no signif - icant increase in the kidney weight. On the other hand, as shown in the present work, daily oral feeding with pirimiphos methyl containing diet lead to induction of vacuolar degenerative changes in the epithelial cells lining renal tubules and scattered glomerular tufts with hyperc - ellularity together with mesangeal cell proliferation. Hettwer`s (1975) in similar experiments reported fatty degeneration. Also, Zaleska-Freljam *et al.* (1983), showed that organophosphates induced stellate shape lumen of the proximal convoluted tubules and vacuolation degenerative changes in the wall of these tubules.

The obtained histopathological changes in the rat's kidney due to pirimiphos methyl may be due to intercellular hypoxia (Hettwer 1975), inhibition of kidney esterase (Rajini *et al*., 1989) and / or to decrease of kidney mucoid content (Awasthi *et al.,* 1984). On the other hand, these changes may occur as an outcome of direct tubular cytotoxicity and / or oxidative stress at the tubular level (Poovala, *et al*., 1999).

In the present work, daily oral feeding with diet containing bendiocarb for 30 days, resulted in mild histopathological changes in kidney tissue. These changes were vacuolation of epithelial lining senal tubules and glomerular tufts. Such could be due to interference with metabolic activities (Fayez and kelgoni, 1992; Pant, *et al*.,1995a and Kackar, 1997).

In conclusion the results of this comparative study emphasize the occurrence of histopathological changes of different severity in testes, liver and kidney of rats as a response to exposure to permethrin, pirimiphos methyl or bendiocarb at the same equivelant of human maximal acceptable daily intake.

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التقييم المقارن للتغيرات الهستوباثولوجيه لسمية كل من البيرمثرين والبريميفوس ميثايل والبنديوكارب على خصية وكليه وكبد الفئران

عفاف نسيم – ناهد باسيلى – سلوى متولى
الهيئة القومية للرقابة والبحوث الدوائية – مصر

مع انتشار استخدام المبيدات الحشرية فى الزراعة والصحة العامة لابد من تكثيف الدراسات على مدى تاثيرها وسميتها للانسان والحيوان . ولقد أجريت دراسات كثيرة على السمية الحادة لهذه المبيدات اما تأثير الجرعات الصغيرة على المدى الطويل فأنها مازالت تحتاج الى دراسات اكثر .

وقد استهدفت هذه الدراسة تتبع التغيرات الهستوباثولوجيه فى كل من الخصى والكليه والكبد بعد تغذية فئران التجارب لمدة 3 يوما على غذاء مضاف اليه كل من البيرمثرين او البريمو فوس ميثايل او البنديو كارب بجرعة مقدارها عشر مرات الجرعة المسموح بها للإنسان والتي مازالت اقل من الجرعة النصف قاتله.

استخدم فى هذا البحث اربعون من ذكور الفئران المهق حيث قسموا الى اربع مجموعات متساوية غذيت المجموعة الضابطة على غذاء الفئران العادي ، اما الثانية فقد غذيت عل نفس الغذاء مضاف اليه 21.739 جزء لكل مليون (ج/م) من البيرمترين وغذيت الثالثة على غذاء مضاف اليه 4.35 من البريموفوس ميتابل ، أما الرابعة فقد غذيت على غذاء مضاف اليه 2 ج/م من البنديوكارب وتم تغذيه الفئران لمدة 30 يوم ذبحت فى نهايتها وتم تحضير قطاعات شمعية من كل من الخصية والكليه والكبد صبغت بالهماتوكسلين والايوسين.

فحصت القطاعات وصورت مجهريا كما تم التقدير الكمى لكل من مدى تثبيط عملية التكوين المنوى واضمحلال خلايا ليدج وتكون الفجوات فى خلال سرتولى فى الخصية اما فى الكبد فقد تم التقدير الكمى لكل من الاضمحلال الفجوى ومعامل الموت الفسيولوجى للخلايا.

وقد أظهرت النتائج ان المبيد الحشري الفوسفورى العضوى بريموفوس ميثايل كان له أسوا الآثار على جميع المظاهر فى جميع الأعضاء تلاه المبيد الحشري من مجموعة الكاربامات (بنديوكارب) وسبب المبيد الحشرى البيرمثرين اقل الاضرار.

ويستنتج من البحث ان التغيرات التى تم دراستها أظهرت مستويات مختلفة من التأثير عند استخدام البيرمثرين والبريميفوس ميتايل والبنديوكارب عند جرعات يمكن ان تتعرض لها الإنسان .