Oral Toxicity of Malathion at Low Doses in Sprague-Dawley Rats: A Biochemical and Histopathological Study

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Abstract

The present study was undertaken to evaluate the sub-chronic toxicity of orally administered low doses of malathion in rats based on the histopathological and biochemical examinations. The study was conducted on sixteen, three weeks old male rats, divided into four groups of four rats of each (three experimental groups and one control group). The rats were treated orally with different doses (0.5, 1and 2 mg/kg) of malathion for 21 consecutive days. After treatment; specimens from liver, brain, and kidneys were taken to investigate the histopathological changes and blood samples were collected for biochemical analysis. The histopathological changes in the liver were mainly represented by parenchymatous degeneration of hepatocytes with mild necrosis, mononuclear cells infiltration in the portal area and severe congestion. However, marked tubular dilation, albuminous casts and hydropic degeneration in tubular epithelium of the cortical and medulla part of the kidney were noticed. Perivascular edema, hemorrhage, spongiosis and early malacia were the most prominent lesions recorded in brain of the treated rats. Biochemical analysis data showed that, the activity of ALT, AST and alkaline phosphatase (ALP) enzymes were increased after treating the rats with malathion at different concentration levels comparing with control. Moreover; the treatment of rats with malathion decreased the activity of acetyl choline esterase (ChE) comparing with control treatment. Also, the kidney function (creatinine) was increased after treatment with malathion comparing to control. The results revealed that, all variations in the histopathological changes and the tested biochemical parameters were dose dependent. Finally, malathion even at low doses induce hazards to rats either by histopathological and the biochemical changes.

Keywords: Malathion, rats, liver, brain, cholinesterase.

Introduction

The hazards of pesticides not only their lethal effect since it was anyhow limited however, their sub-lethal doses considered the source of major concern and this is due to that the most of human and all environment exposed to it. Pesticides which have been emerged as an important environmental problem in the last few decades are causing concern with respect to long-term and low-dose effects of pesticides (endocrine disruption) on public health as well as non-target species.

The use of organophosphorous pesticides (OPs) has increased considerably due to their low potency and durability as compared to organochlorine pesticides. Among OPs, malathion is the most commonly used which is the main cause of most acute pesticide poisonings. Nowadays, the overall pattern of

pesticides use has changed considerably compared with the past; the haz of using such chemicals have been accentuated by the sharp rise in their u agriculture, industry, and by householders (Abdollahi et al., 1995a; Abdolla al., 1995b; Moghadamnia and Abdollahi, 2002).

Malathion is one of the most widely used organophosphate insecti throughout the world. It is used to control pests affecting agricultural c ornamentals, greenhouses, livestock, stored grain, forests, build households and gardens. Contributing to its popularity is its relatively low a mammalian toxicity (Brenner, 1992; Hazarika et al., 2003). However, like pesticides that have been found to cause irreparable damage to human environmental health, malathion may pose a greater risk than the product would lead one to believe. As reported to be mutagenic, a possible carcino implicated in vision loss, causing myriad negative health effects in humar animal studies, damaging non-target organisms, and containing highly impurities, malathion has a legacy of serious problems (Brenner, 1992).

Toxicity of organophosporus used compounds against human and ani were always evaluated by assessment of such biochemical param alterations and histopathological changes in tissues and organs (Enan e 1982; Ghanem et al., 2006). However, there is lack of evaluating the toxic organophosporus at low concentration levels near the environmental level. S most previous studies were using high doses of the tested pesticides. Altho the assessment of enzyme activity in the blood is generally a more sen measure of toxicity than histopathological changes and can be assessed v a shorter time, the tissue alterations considered a confirmatory and suppo diagnostic role in the case of certain abnormalities in blood sampling (Cron et al., 1959).

Therefore, the present study aimed to evaluate the toxic effect of mala at low doses near the environmental levels on the histopathological chang some rat organs (liver, lung, kidney and brain), Moreover, to investigate s biochemical parameters (ALT, AST, ALP, ChE and creatinine) in the tre rats.

2. Materials and methods

2.1. Animal treatment

Adult rats (Sprague dawley) 8 weeks of age and 80-100 gm in we obtained from faculty of medicine, Tanta university were used. Rats housed in polypropylene cages under standard conditions with free acce drinking water and food. The rats were kept in temperature controlled room 14 hrs. light and 10 hrs. dark cycles and were given a standard diet as des by **Korsrud *et al.*, (1972)** and they were given water adlibitum. The ani were randomly divided into three groups each one composed of four ani and treated with malathion for 21days. Malathion was dissolved in almon and was administered to rats through oral route at concentration levels of (and 2 mg/kg body weight). Control group rats were fed with normal containing equal amount of almond oil. After 21 days the rats were sacri under anesthesia. Specimens from kidneys, liver, lung and brain were taker kept in 10% neutral buffered formalin for histopathological examination. blood samples were taken by cardiac puncture in vials containing hep Serum was separated and kept at −20 ◦C for further examinations.

2.2. Necropsy

The necropsy protocol was designed to confirm the presence or absence of lesions associated with malathion toxicity. The necropsy protocol began with observing the external appearance of the carcasses of rats. The carcass was then dissected and a record made of all gross lesions if present. At the time of necropsy, selected tissues were collected for ancillary laboratory tests and for further histopathological examination. Portions of liver, kidney, lung and brain were collected from each carcass and prepared for histopathological examination.

2.3. Histopathological examination:

Samples from the previously mentioned organs were collected and fixed in 10% neutral buffered formalin. Then, the samples were dehydrated in ascending grades of alcohols, cleared in xylen, embedded in paraffin wax, sectioned at 5µm and stained with hematoxylin and eosin (H&E) and then examined by the light microscope (Bancroft and Stevens, 1996). 2.4. Biochemical determinations: Transaminases activity (ALT and AST), ALP, ChE and Creatinine were determined by Bio-diagnostics kits. The colorimetric methods described by Reitman and Frankel (1957), Belfield and Goldberg (1971), Barham and Trinder (1972), Doumas and Watson (1971) and Gornall et al., (1949). The activity of ChE was determined according to the method of Ellman et al. (1961).

2.5. Statistical analysis

The treatments were tested by one-way ANOVA using SPSS statistical software package for windows version 11.0. Duncan's multiple-range test was used to find out the group effects. $P \leq 0.05$ was set as limit of significance.

3. Results and discussion

3.1. Histopathological changes

3.1.1. The histopathological changes in the kidneys:

In the present study, there were slight glomerulonephritis with proliferative endothelial cells of the glomerular tufts of rats treated with malathion at concentration level of 0.5 mg/kg (Fig. 1), but in those rats treated with malathion at concentration level of 1 mg/kg the kidney showed slight nephrotic changes, characterized by presence of somewhat enlarged renal tubules lined with large cells of pale cytoplasm and vesicular nuclei (Fig. 2). In rats treated with malathion at concentration level of 2 mg/kg, the pathological changes appeared to be marked than those observed in the rats treated with malathion at concentration level of 0.5 and 1 mg/kg. Kidneys showed interstitial nephritis with slight interstitial mononuclear cell infiltration (Fig. 3), marked cell swelling and cloudy appearing epithelial cell lining of the renal tubules forming star shape like lumens (Fig. 4), renal casts (Fig. 5) and severe plugging of the lumens of the renal tubules with proteinaceous casts (Fig. 6).

Kidneys are responsible for the elimination of metabolic waste products and the control of the amount and composition of the body fluids. Nephrotoxicity may lead to systemic toxicity causing decreased ability to excrete body wastes, inability to maintain body fluid and electrolyte balance and decreased synthesis of essential hormones (e.g., erythropoietin) (Finn, 1977). The present results showed that different doses of malathion induced histopathological changes in the kidney of rats. Marked tubular dilation, hydropic degeneration in tubular epithelium, moderate congestion and hemorrhage in both the cortical and medullary parts of the kidneys were recorded. Kerem et al., (2007) reported

some tubular dilation, renal casts and atrophy in the cortex of male Wiste exposed to mild doses of fenthion (25 or 50 mg/kg). Meanv parenchymatous degeneration of cells of renal tubules was observed in dose fenthion groups (75 or 100 mg/kg). Afshar et al., (2008) also, rep some histopathological changes in the kidneys of rats as marked tubular dil hydropic degeneration in tubular lining epithelium, cloudy swelling, mod congestion and hemorrhage in the cortical and medullary parts of the ki after treatment with different doses of the organophosphate pes fenitrothion. Histopathologic examination of the liver and kidney indicat significant injury in rats receiving 1 and 2 mg/kg malathion and histopathological changes were dose dependent which agreed with findin Kerem et al., (2007) and Afshar et al., (2008).

3.1.2. The histopathological changes in the liver:

In the rats treated with malathion at concentration level of 0.5 mg/k liver showed mild perivascular mononuclear cell infiltration (Fig. 7) sinusoidal cell activation with increased number of kupffer cells in the he sinusoids (Fig. 8), congestion and dilatation of the hepatic sinusoids (Fig. 9 slight fatty change in the cytoplasm of the hepatocytes with the presen small vacuoles of clear lumens and sharp outlines (Fig. 10). These cha were nearly appeared of the same degree in those rats treated with malathi concentration level of 1 mg/kg, except for the sinusoidal cell activation v became of moderate degree (Fig. 11) and the hepatic lobules showed ma peripheral cytosolic hydrop with vacuolated cytoplasm of the hepatocytes 12). Meanwhile; the inflammatory reaction in the liver of rats treated malathion at concentration level of 2 mg/kg, became more severe in the fo granuloma like reaction with focal collection of kupffer cells (Fig. 13), focal a of hepatocellular coagulative necrosis with infiltration of mononuclear cells a margin of the necrosed areas (Fig. 14).

The liver is well known target organ of the toxic impact regardir function in biotransformation and excretion of xenobiotics (Roganovic-Zaf and Jordanova, 1998). The liver is particularly susceptible to xenobiotics d a large blood supply and its role in metabolism. In this study, after administration of different doses of malathion, histopathological changes observed in the liver of rats in all treated groups compared to the control g Our results showed that the histopathological changes in the liver were dependent and the histopathological changes observed clearly with the increase. The effect of organophosphorous insecticides and other pesticide the liver of experimental animals were studied by many investigators. Tos et al., (2003) found that exposing male Wistar rats to different dose malathion induced histopathological changes in the liver. The oral administr of the single dose of malathion, caused degenerative changes in the liver i form of parenchymatous degeneration in 80% of animals (Tos-Luty et al., 20 The recorded results in this study agree with that of Morowati, (1997); Gc al., (2005); Gokcimen et al., (2007); Sayım, (2007); Yehia et al., (2007) revealed that OP insecticides are known to induce various histopatholo changes in the liver tissue and indeed they found by light microscopic anal that malathion induced inflammatory cell infiltration, hemorrhage, calcifica vacuolar degeneration, dilation of sinusoids, vascular congestion and necro the rat liver. These changes are entirely consistent with the changes in va

biochemical parameters that were also observed. Such liver damage may arise from the toxic effects of malathion, which disturbs the detoxification mechanisms of the liver. In addition, it is possible that malathion, like several other insecticides, adversely affects the cytochrome P450 system or the mitochondrial membrane transport system of hepatocytes **(Gokcimen *et al.*, 2007).**

3.1.3. The histopathological changes in the brain:

There were no obvious changes recorded in the brain of rats treated with malathion at concentration level of 0.5 mg/kg, but in those rats treated with malathion at concentration level of 1 mg/kg the brain showed few hemorrhagic areas in the parenchyma of brain (Fig. 15). In the rats treated with malathion at concentration level of 2 mg/kg the brain lesions became more pronounced in the form of moderate perivasular edema (Fig. 16) moderate cerebral hemorrhages (Fig. 17) and cerebellar hemorrhages (Fig. 18), marked perivascular and pericellular edema (Fig. 19), marked cerebellar spongiosis (Fig. 20), neuronal cell degeneration (Fig. 21) and features of focal early malacia in the cerebral cortex with neuronal ischemic injury (Fig. 22). The damage of brain rats after malathion oral administration had been reported (Hazarika et al., 2003). Edema was a prominent finding in the brain of high malathion dose treated groups which may be due to the effect of malathion on the endothelial cells of the blood capillaries; consequently, increases the permeability of these capillaries and leakage of the proteinaceous transudate this is in agreement with Goyer and Rhyne, (1973). We found that the brains of the high-dose of malathion (2mg/kg) groups in our study showed spongiosis of the cerebral and cerebellar white matter and ischemic neuronal injury in cereberal cortex. The pattern of such microscopic changes in the high dose groups were similar to changes reported previously by Goetz and Washburn, 1999 and Gurer and Ercal, 2000.

3.2. Biochemical analysis

3.2.1. Effect on liver enzymes

The obtained data in table (1) showed that, the activity of ALT, AST and ALP were increased after 21 days of rats administration with malathion at different concentration levels (0.5, 1 and 2 mg/kg) comparing with control treatment that means; the increase of these enzymes activity was positively correlated with malathion doses. In the present study, the increase in liver functions enzymes activities (ALT, AST and ALP) after treatment of rats with malathion agreed with the findings of (Bogusz (1968); Menratha et al., (1973); Abdel-Rahman et al., (1985) Agrahari et al., (2007).

In general the liver is oftenly the primary target organ for the toxic effect of xenbiotics; therefore it can be used as an index of toxicity of various toxicants. Transaminases are important critical enzymes in biological processes since they play a role in amino acids biosynthesis and consequently they considered specific indicators of the liver damage.

Acid phosphatase is a lysosomal enzyme that hydrolyses the phosphorous esters in acidic medium. Thus, it is logic that the enzyme is hydrolytic in its function and acts as one of the several acid hydrolases in the autolysis process of the cell after its death. Alkaline phosphatase splits various phosphorous esters at alkaline pH and its activity is related to cellular damage. The significant difference in phosphatases activities between the control and experimental groups of rats following the exposure of malathion might be considered due to the damage of hepatic tissue with disturbed normal liver function. This is agree

with findings of many researches who reported that, when the liver membrane is damaged, several enzymes located in the hepatocyte cyt including ALT, AST and ALP are secreted into the blood (Ncibi et al., 2(Consequently, these enzymes are considered as markers of liver dan (Gokcimen et al., 2007). Moreover, It has been shown that OPs insecticides elevate the enzymatic activities of ALT, AST and ALP (Khan et al., 2005; Og et al., 2008; Ncibi et al., 2008; Celik et al., 2009; Rezg etal., 2008).

The transaminase ALT and AST (entering the blood after the cell nec of certain organs) can be used to establish the tissue damage of the liver. Ir study, we found that the malathion-treated animals had significantly higher AST and ALP levels than the control group animals and this is confirme histological changes found in liver tissue and agree with the findings of Agr et al., (2007) who recorded the same results with an organophosp compound. Therefore, the elevation of liver enzymes in rats treated malathion might be due to the early damage in the hepatic cells and positively correlated with the histopathological changes in the liver tissue ir study.

3.2.2. Effect of malathion on brain function

Referring to cholinesterase activity as a brain function, the obtained re revealed that the activity decreased at all concentration levels of mala comparing to the control treatment. The reduction in the enzyme activity rel to control after treatment with malathion was dose dependent. These re agreed with findings of many researchers who reported that the most prom clinical effects of poisoning with OPs are related to their inhibition of the ac of blood cholinesterase (ChE) (Timur et al.2003 and Hazarika et al., 2003).

3.2.3. Effect of malathion on kidney functions

Regarding to the kidney functions, creatinine and albumin levels increased at all concentration levels of malathion treated rats comparir control ones. Moreover, as the same with other biochemical parameters creatinine and albumin levels were increased with increasing in malathion d (Mohssen , 2001). The increase of creatinine and albumin level in rats tre with malathion comparing to control treatment assumed to be due to the dan in kidney. Moreover, the histopathological changes in kidney tissue suc inflammation, severe plugging of lumena of renal tubules with albuminous c confirm this explanation. These results agree with that pointed out by Kas (1971) and Varley et al. (1980), they reported that the creatinine excreti dependent almost entirely on the process of glomerular filtration, although tul secretion contributes slightly. The slight but significant rise in the s creatinine level points out the impairment of the glomerular function and tul damage in the kidneys.

4. Conclusion

The results showed a significant increase in ALT, AST, APT and creat while, significant reduction in cholinesterase activity was recorded in the after treatment with malathion at different dose levels. The disruption ir biochemical parameters after treatment with malathion were confirmed by cl histopathological changes in liver, brain, lung and kidney of the rats. The re also confirmed that the toxicity of malathion on treated rats was dose depen Even this study did not showed high toxicity of malathion at this concentr levels of malathion but still recorded toxicity of malathion that can be a sour

major concern for human health with the respect of long time and low dose exposure. Therefore, we suggest that similar studies should be done on different pesticide compounds at different low concentration, close to environmental level. Since, the recorded toxicity of malathion and possibly other compounds at these low concentration levels could urge the Egyptian governments for more restrictive regulations about these compounds levels.

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Table (1) Effect of malathion at different concentration levels on some biochemical parameters in rat.

Concentration level	ALT	AST	ALP	ChE	Creatinine mg/di
0.5	17.66 c	13.58 c	2.897b	0.872×10^{-4}b	0.343 b
1	17.97b	13.98b	3.166 a	0.752×10^{-4}a	0.356 b
2	21.39a	14.98a	3.177 a	0.671×10^{-4}a	0.450a
Control	17.76c	13.44d	2.798b	0.946×10^{-4}b	0.322c

Figure Legend

(Fig.1). Kidney of rats treated with 0.5 mg/kg malathion showing mild proliferative glomerulitis: hypercellularity due to proliferation of mesangial, endothelial and epithelial cells of the glomerular tufts (H&E, X200).

(Fig.2): Kidney of rats treated with 1 mg/kg malathion showing slight nephrotic changes. Enlarged renal tubules lined by large size cells of pale cytoplasm and vesicular nuclei (H&E, X200).

(Fig.3): Kidney of rats treated with 2 mg/kg malathion interstitial nephritis with slignt interstitial mononuclear cell infiltration (H&E, X200).

(Fig.4): Kidney of rats treated with 2 mg/kg malathion showing marked cloudy swelling. The epithelial cell lining of the renal tubules are swelled and cloudy forming star shape like lumens (H&E, X200).

(Fig.5): Kidney of rats treated with 2 mg/kg malathion showing renal casts. Homogenous pink material present in the lumen of renal tubule and is compressing the adjacent tubules (H&E, X200).

(Fig.6): Kidney of rats treated with 2 mg/kg malathion showing severe plugging of the lumens of the renal tubules with proteinaceous casts (H&E, X400).

(Fig.7): Liver of rats treated with 0.5 mg/kg malathion showing mild perivascular mononuclear cell infiltration (H&E, X100).

(Fig.8): Liver of rats treated with 0.5 mg/kg malathion showing mild sinusoidal cell activation with increased number of kupffer cells in the hepatic sinusoids (H&E, X100).

(Fig.9): Liver of rats treated with 0.5 mg/kg malathion showing congestion and dilatation of the hepatic sinusoids (H&E, X100).

(Fig.10): Liver of rats treated with 0.5 mg/kg malathion showing slight fatty change in the cytoplasm of the hepatocytes with the presence of small vacuoles of clear lumens and sharp outlines (H&E, X200).

(Fig.11): Liver of rats treated with 1 mg/kg malathion showing moderate sinusoidal cell activation with increased number of kupffer cells in the hepatic sinusoids (H&E, X200).

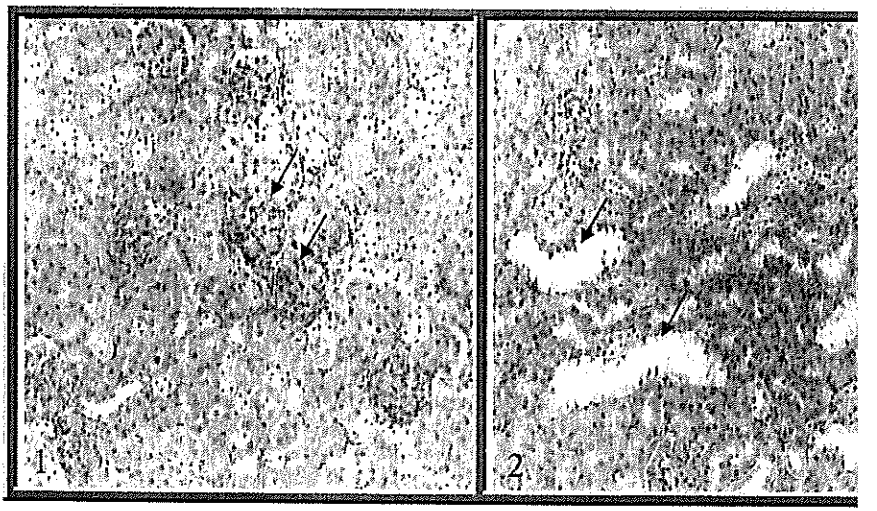
(Fig.12): Liver of rats treated with 1 mg/kg malathion showing marked peripheral cytosolic hydrop with vacuolated cytoplasm of the hepatocytes (H&E, X50).

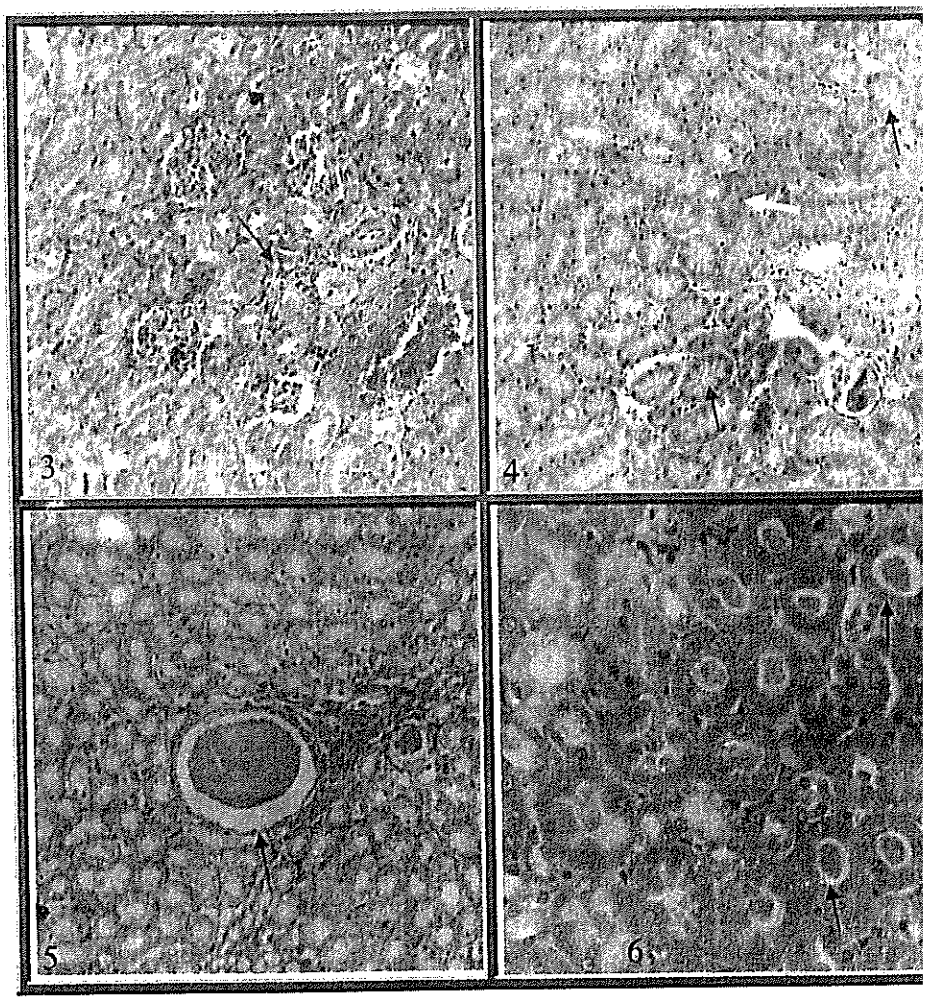
(Fig.13): Liver of rats treated with 2 mg/kg malathion showing granuloma like reaction with focal collection of kupffer cells (H&E, X400).

(Fig.14): Liver of rats treated with 1 mg/kg malathion showing focal areas of hepatocellular coagulative necrosis with infiltration of mononuclear cells at the margin of the necrosed areas (H&E, X100).

(Fig.15): Brain of rats treated with 1 mg/kg malathion showing hemorrhagic areas. RBcs were scattered outside the blood vessels in the parenchyma of brain (H&E, X100).

(Fig.16): Brain of rats treated with 2 mg/kg malathion showing mode perivasular edema (H&E, X100).
(Fig.17): Brain of rats treated with 2mg/kg malathion showing moderate cere hemorrhages (H&E, X100).
(Fig.18): Brain of rats treated with 2 mg/kg malathion showing cereb hemorrhages (H&E, X100).
(Fig.19): Brain of rats treated with 2 mg/kg malathion showing mar perivascular and pericellular edema (H&E, X100).
(Fig.20): Brain of rats treated with 1 mg/kg malathion showing mar cerebellar spongiosis (H&E, X200).
(Fig.21): Brain of rats treated with 2 mg/kg malathion showing neuronal degeneration.The nucleiof the neuronal cells appeared small and pyknotic (H X200).
(Fig.22): Brain of rats treated with 2 mg/kg malathion showing features of f early malacia in the cerebral cortex with neuronal ischemic injury (H&E, X400

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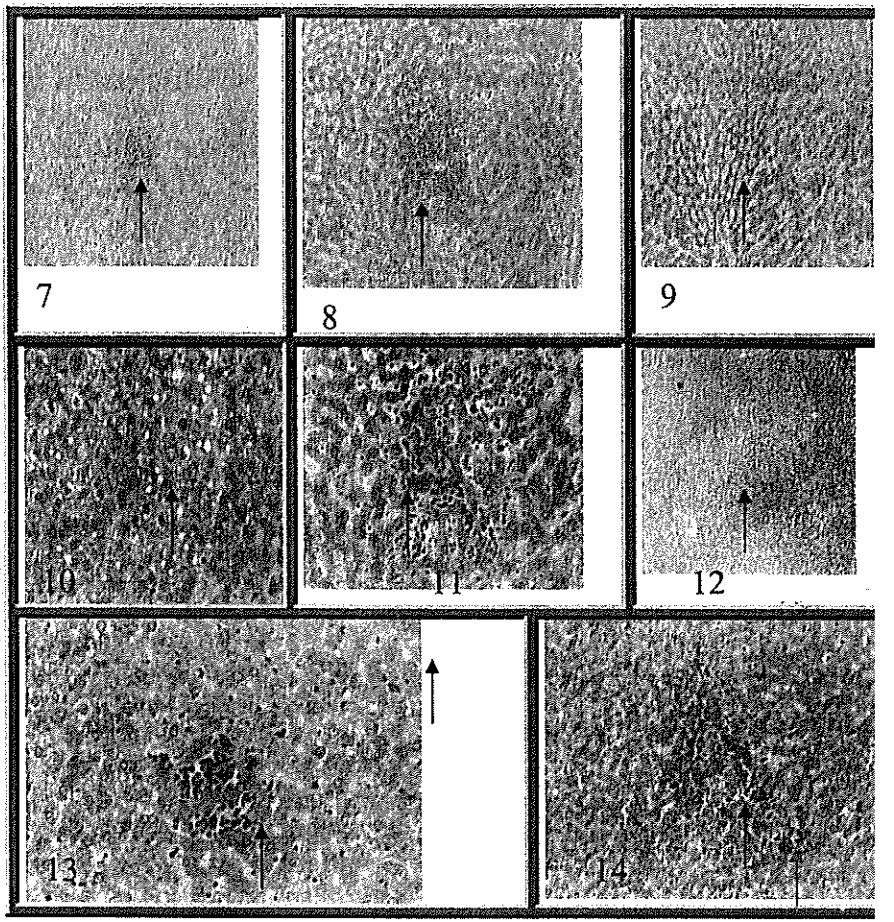
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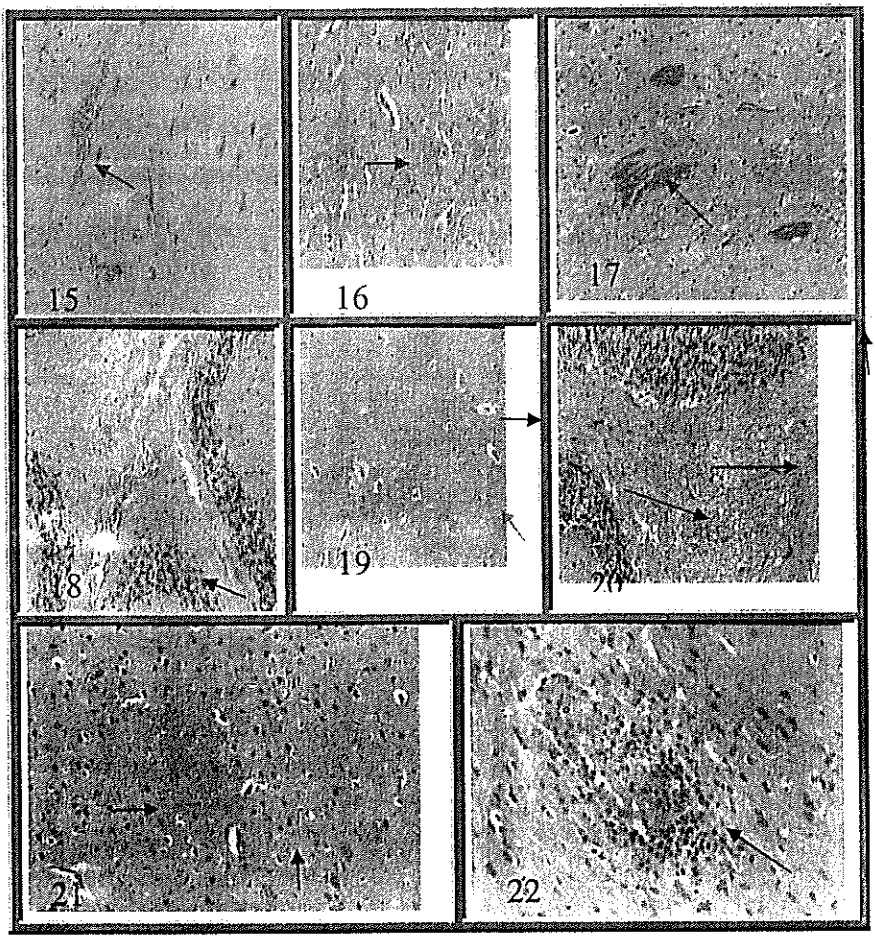
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ص العربى

جريت هذه الدراسة لتقييم التسمم الفرعي المزمن لمادة الملاثيون في الفئران عن طريق الفم بإعطاء جرعات
لفترة بسيطة استنادا إلى دراسة الكيمياء الحيوية والباثولوجيا. وأجريت الدراسة على الفئران
ر عمر ثلاثة أسابيع، وقسمت إلى أربع مجموعات (ثلاث مجموعات تجريبية و واحدة
رعة التحكم). وعولجت الفئران عن طريق الفم بجرعات مختلفة (٠,٥ ، ١ ، ٢ مغ / كغم)
ملاثيون لمدة ٢١ يوما متتاليا. بعد المعالجة ، تم أخذ عينات من الكبد والمخ والكلى والرئة
ن التغيرات النسيجية في هذه الأعضاء ثم تم جمع عينات من الدم للتحليلات البيوكيميائية
لعلاج بالملاثيون. و تمثلت الإصابات الباثولوجية للكبد في وجود ضمور و تنكرز في
الكبد و ارتشاح خلايا التهاب وحيدة النواة في المنطقة البابية و في الكلي تمثلت في اتساع
ت الكلي ووجود احتشاء في تجويف انيبات الكلي و في المخ تمثلت الإصابات في صورة
احات مائية حول الأوعية الدموية و الخلايا العصبية كذلك و جود انزفة في كلا من المخيخ
خ و تنكرز في الخلايا العصبية في المخ. وأظهرت النتائج زيادة ملحوظة في تحليل
ت البيوكيميائية في الفئران المعالجة بالملاثيون بتركيزات مختلفة مع انخفاض نشاط أستيل
ن استريز مقارنة مع الفئران في مجموعة التحكم. كذلك لوحظ زيادة في وظائف الكلى بعد
ج مقارنة مع مجموعة التحكم. وكشفت النتائج أن جميع الاختلافات في معايير الاختبارات
كيميائية والباثولوجيا كانت تتناسب طرديا مع تغير الجرعة. و لقد أكدت التغيرات
لوجية في أنسجة الكبد والمخ والكلى مثيلتها البيوكيميائية وعلي الرغم من عدم وجود
ات سمية كبيرة عند استخدام جرعات الملاثيون المختلفة في التجربة إلا أن النتائج التي
نا عليها تؤكد أن الملاثيون مازال خطرا يهدد الإنسان عند استعماله بجرعات أكبر و لوقت
. لذا نقترح دراسات مماثلة للآثار السمية المترتبة علي استعمال المبيدات الحشرية
جودة في مصر عند الجرعات المسموح بها عند استعمالها لفترة طويلة.