© by PSP Volume 31– No. 08/2022 pages 7861-7868 Fresenius Environmental Bulletin

TOXICOLOGICAL EVALUATION OF A MONOAMMONIUM PHOSPHATE FERTILIZER IN RATS FOLLOWING 30 DAYS OF REPEATED ORAL EXPOSURE

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ABSTRACT

The present study was undertaken to evaluate the subacute toxicity of a synthetic fertilizer widely used in agriculture (Phosfert®, monoammonium phosphate $NH_4H_2PO_4$ (MAP)) on some haematological and biochemical profiles as well as liver and kidney histology in Wistar rats. MAP was administered to rats orally at 200, 400, and 800mg/kg of body weight doses for 30 days. Results showed decreased body weight and a significant increase in liver and kidney relative weights in MAP-treated rats. In addition, hematotoxicity effect of high doses of MPA was evidenced by decreased levels of red blood cells (RBC), haemoglobin (Hb) and hematocrit (Ht) along with increased levels of white blood cell (WBC) counts. Further, hepatic and renal markers and lipid profiles were markedly increased however; total proteins and albumin levels were considerably decreased in MAP treated rats as compared with controls. These effects were supported by the liver and kidney histopathological evaluations. Conclusively, the study proved that the long-term use and at higher doses of MAP may cause adverse hepatic and renal effects

KEYWORDS:
Subacute toxicity, Monoammonium phosphate, Rats, Liver, Kidney

INTRODUCTION

Phosphorous is an essential nutrient element for plant growth, whose environmental deficiency is a limiting cultivation factor. As a result, phosphorous fertilization is mainly used to avoid soil phosphorous deficiency and to improve plant growth and yield [1].Additionally, the mineral fertilizer phosphates lead to increase agricultural returns and contribute to feeding the world population [2].They are wide-world used fertilizer [3, 4] due to their crucial role in providing one of the most important nutrient elements for crop production. In fact, around of 150millions tonnes of phosphate rocks are mined annually throughout the world for the production of PO_4 fertilizers [5, 6]. The excessive use of synthesized fertilizers and pesticides can contribute to improving the yield of cultivation, and consequently can contaminate the soil, water and air resulting in serious human and environmental hazards [7, 8, 9]. Farmers and inhabitants living close to farms or factories producing chard, and consumers are all therefore exposed to these chemicals [10]. Human exposure to ammonium phosphate salts can be occurred through dermal contact during their uses in cosmetics, flame retardants, and fertilizers, or through ingestion via their uses as food additives and plant nutrients [11]. Moreover, MAP is one of the main phosphate fertilizers in the world, produced by reactions of ammonia and phosphoric acid resulting in the formation of the monobasic salt [12].Also, It is relatively unstable due to the reason that the ammonium hydroxide is a very weaker base than those of the metallic hydroxyls, and the ammoniac can avoid being as a gas form [13]. Toxicological data of MAP revealed its weak toxicity via pulmonary, oral, and skin exposures, in addition to its non-irritant or largely irritant effects during skin or eye exposure [11].Nevertheless, the chemical can cause several effects on human and animal health, and so the continuous exposure may result in alterations of various vital functions of the body. On the other hand, previous studies investigating the sub-chronic exposure of experimental animal models to MAP have shown submucosal stomach inflammation, thickening of the stomach wall, and horizontal strip/teeth [14,15, 16].Since up to now no research study investigating the effects of higher doses of MPA on reproduction or development has been conducted, therefore the present study is the first to evaluate the toxic effects of MAP, the widely used fertilizer in Algeria, on some biochemical markers and liver and kidney histology in rats.

MATERIALS AND METHODS

Chemical Materials. Phosfert®, monoammonium phosphate (CAS N° 7722-76-1) was purchased from a company named Profert Fertilizers of Bejeia, Algeria.

Biological material. Twenty-eight male Wistar rats weighing 240-280g obtained from Pasteur Institute of Algiers, Algeria were placed in plastic cages and maintained in the animal house of our Institution (22±3°C, natural photoperiod, and relative humidity of 50±10%). Animals were given water and food ad libitum. All experimental procedures were carried out in accordance with our institution's Animal Care Committee and Ethics Committee (AFRO. No 478, 2009).

Experimental design. After three weeks of the acclimation period, rats were divided into four main groups (7 rats/group) namely, control untreated group received water as a vehicle, and three treated groups (MAP 1, MAP 2 and MAP3) received respectively MAP orally 200, 400 and 800 mg /kg body weight for 30 days. MAP was dissolved in mineral water before administration to animals. At the end of the treatment period, rats were sacrificed and blood samples were collected in EDTA and sec tubes to evaluate the hematological and biochemical parameters. The liver and kidney of each rat were removed by transverse abdominal incision and immediately weighed.

Hematological and biochemical evaluation. Hematological parameters (red blood cell (RBC), white blood cell (WBC), hemoglobin (Hb), hematocrit (Ht), platelets (PLT), mean corpuscular volume of red blood cells (VGM), and mean corpuscular hemoglobin concentration (MCHC)) were evaluated using BC-30 analyzer (Mindray), while biochemical parameters (glucose, cholesterol, triglycerides, transaminases (ASAT and ALAT), alkaline phosphatase (ALP), total proteins, albumin, urea, creatinine, and uric acid) were spectrophotometrically measured using commercially available kits (SARL Diagnopharm).

Histopathological evaluation. Kidney and liver sections were fixed in 10% formalin, dehydrated in 70-100% ethanol series, and embedded in paraffin baths at 58°C. Then, tissue specimens of 4-6 mm were prepared from paraffin blocks using a rotary microtome. The staining process of tissue specimens was performed by Hematoxylin-Eosin (H-E) as described elsewhere [17]. Tissue images were photographed using an optical microscope (OPTIKA B-290, Italy).

Statistical analysis. Results were tested for the statistical significance of the differences between the treatments and untreated control group by the t-Student test to compare using the SPSS Statistics 23.0 program, where $p < 0.05$ was considered significant. Results were displayed as mean ± standard deviation (SD).

RESULTS

Effects of treatments on physiological aspects. As shown in Table1, the body weight gain was significantly decreased in high dose (800mg/kg) MAP treated rats for 30 days as compared to untreated controls. Whilst, the relative liver, and kidney weights were significantly increased in MAP treated group. The increased in relative weights of these organs were remarkably higher in rats receiving MAP at 400 and 800 mg/kg doses (MAP2 and MAP3) than those receiving MAP at 200mg/kg dose (MAP1) showing no significant changes.

Effects of treatments on haematological parameters. Table 2 depicts significant increase in white blood cells (WBC) counts and mean corpuscular volume (VGM) along with, a significant decrease in red blood cells (RBC) counts, hemoglobin (Hb) and hematocrit (Ht) levels in high dose MAP exposed rats as compared, to the controls. No significant changes were observed in platelet count (PLT) and mean corpuscular hemoglobin concentration (MCHC) MAP groups when compared with the control group.

TABLE 1
Change in body weight, liver- and kidney- body weight ratios in control and treated rats.

Parameters	Treatments			
	Control	MAP1	MAP2	MAP3
Initial weight (g)	256,14±6,28	256,00±5,42	256,86±4,18	257,00±6,48
Final weight (g)	289,43±6,24	289,71±7,04	286,00±5,29	277,00±9.22**
Weight gain (%)	33,29±10,06	33,71±5,31	29,14±5,40	20,00±4,62**
Relative liver weigh (g/100 g b.w.)	2,70±0,14	2,79±0,16	3,00±0,17**	3,60±0,14***
Relative kidney weight (g/100 g b.w)	0,23±0,01	0,24±0,02	0,25±0,01**	0,28±0,02***

**p < 0,01 ; ***p < 0,001: Significant difference compared with the control group

TABLE 2
Change in hematological parameters in control and treated rats (MAP1, MAP2 and MAP3) for 30 days (data are given as mean ± SD).

Parameters	Treatments			
	control	MAP1	MAP2	MAP3
WBC	7,54±0,83	7,47±0,56	8,47±0,54*	8,89±0,38**
RBC	8,90±0,41	8,67±0,51	8,27±0,37**	7,75±0,26***
Hb	16,84±0,53	16,56± 0,53	15,90± 0,75*	15,73±0,34***
Ht	45,36±0,67	44,93±1,07	43,89±0,94**	42,54±0,49**
PLT	578,43±44,55	572,86±81,83	559,29±47,42	556,14±43,23
VGM	50 ,99±2,56	51,98±3,10	53,15±1,70	54,97±2,36**
CCMH	37,14±1,25	36,86±1,19	36,25±2,05	36,98±0,89

*p < 0,05 ; **p < 0,01 : Significant difference compared with the control group

TABLE 3
Changes in the lipid profiles and liver functional markers of the control and treated rats (data are given as mean ± SD).

Parameters	Treatments			
	Control	MAP1	MAP2	MAP3
Glucose (g/l)	1,12± 0,07	1,15±0,06	1,21±0,05**	1,29±0,05***
Cholestrol (g/l)	0,96±0,08	0,97±0,06	1,08±0,05**	1,24±0,03***
Triglycerides (g/l)	0,68±0,13	0,70±0,08	0,75±0,07	0,85±0,04**
ASAT (U/L)	114,64±16,29	119,33±11,08	132,56±14,53*	149,76±9,84***
ALAT (U/L)	67,60±9,03	65,74±8,79	79,81±8,51*	84,60±5,97**
ALP (U/L)	117,16±5,46	124,34±12,82	132,18±8,07**	139,82±3,16***
Total protein (g/L) (g/l)	71,17±5,18	67,16±6,56	58,38±5,01***	62,89±3,02***
Albumin (g/l)	36,00±1,58	35,00±0,44	34,03±0,27**	33,17±0,53**

*p < 0,05 ; **p < 0,01 ; ***p < 0,001 : Significant difference compared with the control group.

TABLE 4
Changes in kidney functional markers of control and treated rats (data are given as mean ± SD).

Paramètres	Treatments			
	Control	MAP1	MAP2	MAP3
Urea (mg/dL)	40±02	40±03	43±03*	45±03**
Creatinine (mg/dL)	1,17±0,10	1,19±0,08	1,26±0,06*	1,38±0,06**
Uric acid (mg/dL)	4,75±0,54	4,55±0,67	5,15±0,65	5,74±0,52**

*p < 0,05 ; **p < 0,01 : Significant difference compared with the control group

Effects of treatments on biochemical parameters. Table 4 shows a significant increase in serum glucose level in MAP2 (400 mg/kg) and MAP3 (800 mg/kg) treated rats with no change in MAP1 (200 mg/kg) treated rats. Lipid profiles (cholesterol and triglycerides) were increased significantly in MAP2 and MAP3 groups (400 and 800 mg/kg), since MAP1 (200mg/kg) group shows no change in these parameters as compared to the control group. Further, biochemical liver enzyme markers show a significant increase in serum transaminases (AST/ALT) and alkaline phosphatase (ALP) activities in MAP2 and MAP3 treated rats, and no changes in MAP1 treated rats compared with controls. Whilst, total protein, and albumin levels were significantly decreased (Table 3) in MAP2 and MAP3 groups, and on contrary urea, creatinine, and uric acid levels were significantly increased in all treated groups as compared to control group (Table. 4).

Liver histopathology: The liver histology of untreated control rats revealed a regular histological architecture containing hepatocytes (H) separated by sinusoids (S), centrilobular veins (VC) (Figures. 1A, 1B), and similarly, no histological changes were found in the liver of the MAP1-treated group in comparison with the control group. However, marked liver histological alterations evidenced by hepatic suffering, sinusoidal congestion, an inflammatory portal infiltrate (Figures.1C, 1D), vascular congestion, and dilatation of the centrilobular vein (Figure 1E), in addition to slightly vacuolated cytoplasm with few lipid droplets (Figure 1F) were observed in MAP2 and MAP3 treated rats.

Kidney histopathology. Microscopic observation of renal tissues in control rats revealed normal structure of renal glomeruli and tubules (Figure 2.A). Similarly, no histological changes were noticed in MAP1 treated rats (Figure 2B). On the other hand, histological sections in MAP2 and MAP3 treated rats (400 and 800 mg/kg/day) showed remarkable changes in the glomeruli and tubule structures as evidenced by glomeruli hypertrophy, vascular congestion and dilation of the tubular lumen (Figures 2C, D).

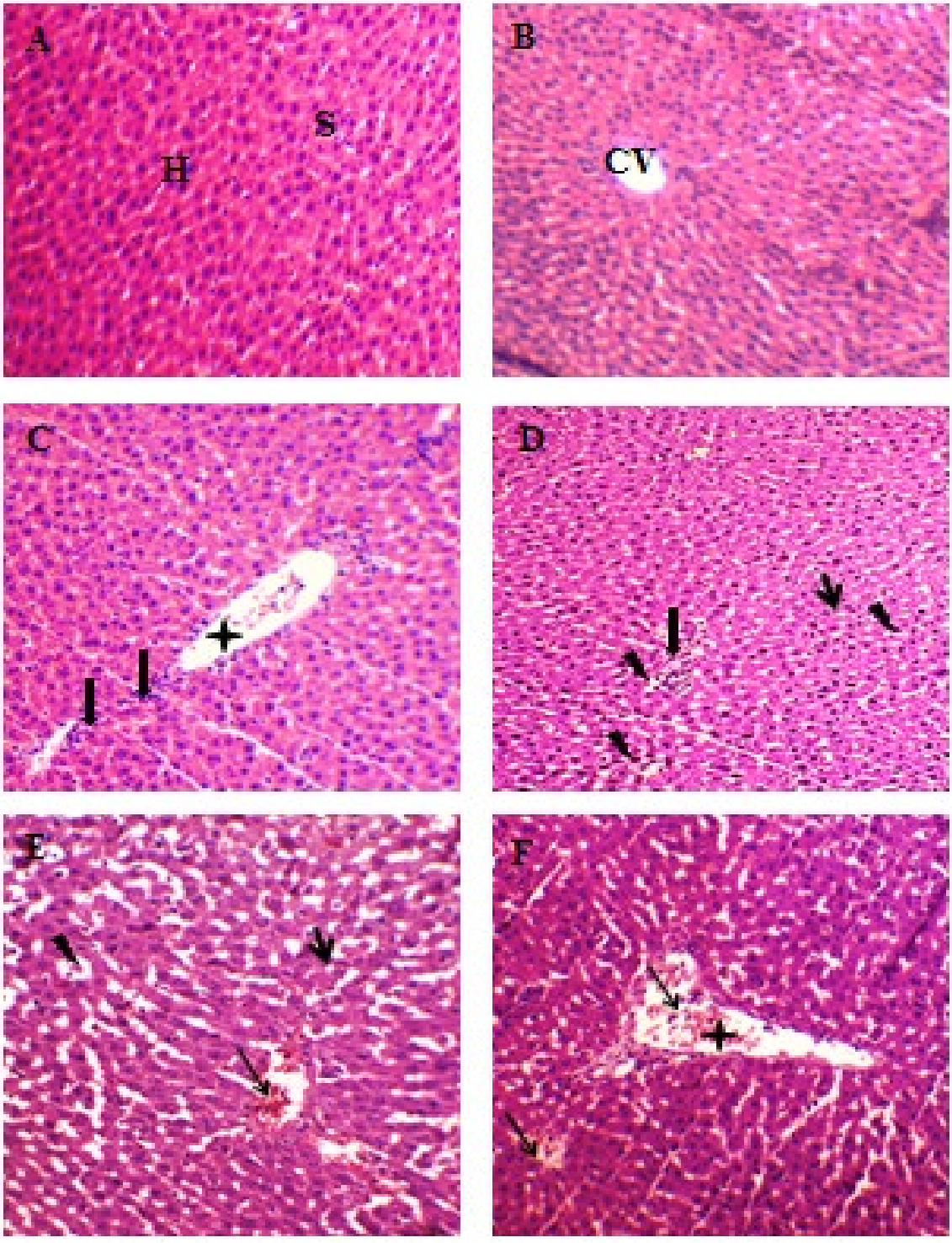

FIGURE 1

Histological sections of HE- stained liver tissue from control and treated rats. Liver tissues from the control group revealed normal and preserved histoarchitecture (A, B). The damage in hepatic tissues (C-F) induced by MAP increases in a dose dependent manner (Gr. 100X).

S, sinusoids; H, hepatocyte; CV, central vein; leucocyte infiltrations; dilated central vein; vacuoles; haemorrhage; degenerated hepatocyte.

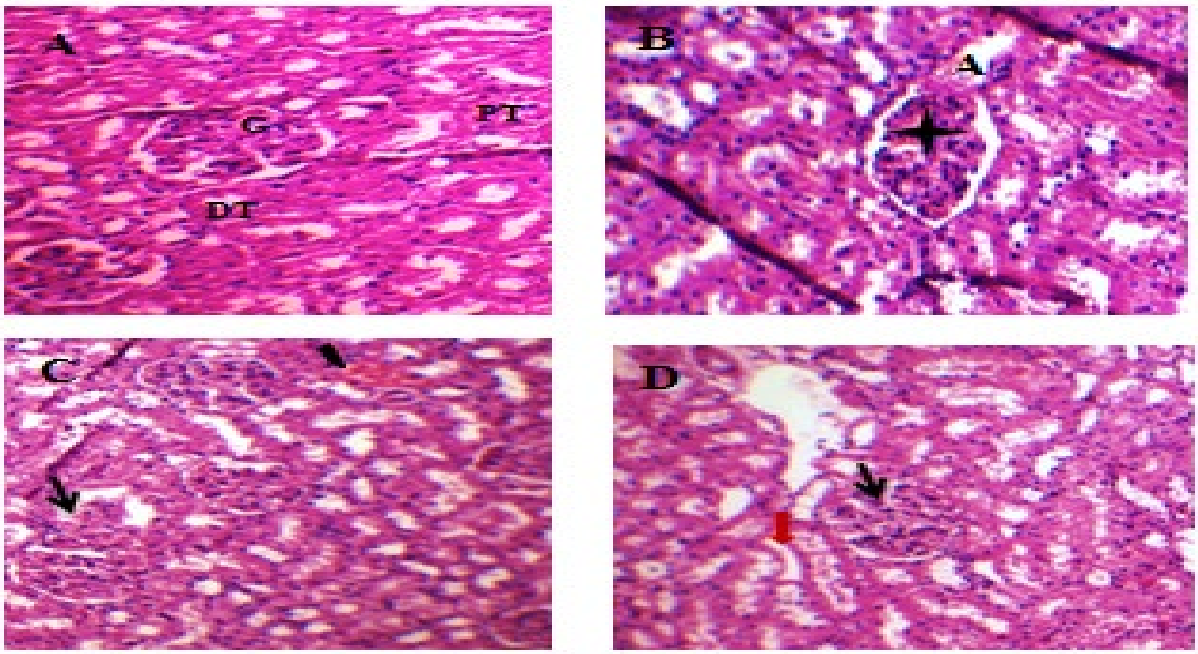

FIGURE 2

Histological sections of HE- stained kidney tissue from control and treated rats. Kidneys from control rats revealed normal and preserved histoarchitecture (A, B).

Kidney sections from MAP-treated rats showed increased tissue damage in a dose dependent (C-D) (Gr.100x).
✦ Lipid vacuolation; ↘ glomeruli hypertrophy; ↖ vascular congestion; ↓ dilation of the tubular.

DISCUSSION

The excessive and uncontrolled agricultural use of chemicals, including fertilizers, herbicides, and insecticides leads to a fearsome rise in the frequency of diseases like cancers, cardiovascular diseases, respiratory disorders, etc. [18]. Monoammonium phosphate (MAP) is a fertilizer commonly used to enhance agricultural production, but its repeated application causes the accumulation of harmful metals in plants and soil throughout time [19]. Thus, the conducted experimental study based on the variation of the major biochemical liver and kidney markers, haematological profiles, as well as body weight in MAP exposed rats. In this study, treatment with MAP caused dose dependent body weight decrease as compared to the control group. As reported [20], body weight is an important indicator in assessing the toxic effects of chemicals on the physiological aspects of experimental animals. In accordance with our finding, the decrease in body weight of chemically exposed animals has been reported [21; 22]. Also, results showed a significant increase in liver and kidney relative weights in MAP treated groups compared with the control. Similarly, the liver and kidney relative weights were increased in MAP exposed freshwater fishes [23]. This is likely due to the organ hypertrophy on the one hand, and the intensified chemical accumulation in organs, on the other hand. Unlike this finding, a previous study [24] conducted on Diammonium Phosphate (DAP) exposed birds has reported a decreased liver and kidney relative weights in birds exposed to 10% DAP for 30days. As the haematological parameters are the early indicator of the chemical toxicity on these soft organ tissues [25], the study examined the variations in the haematological profiles following MAP treatment. Here, MAP was found to induced a macrocytic anaemia evidenced by a significant decrease in red blood cells (RBC) counts, and the levels of haemoglobin (Hb) and haematocrit (Ht) with a significant increase in mean cell volume (MCV) and no change in mean corpuscular hemoglobin concentration (MCHC). In addition, white blood cell (WBC) counts were significantly increased following MAP treatment and this concords with the study investigating the toxicity of calcium nitrate in rats. This may indicate the activation of the animals' immune system toward the chemical-induced tissue inflammatory reactions [26]. Similar haematological changes have been also reported in the study conducted on DAP-exposed birds [24], and in Mancozeb exposed rats [27]. In this study, serum glucose level was significantly increased in MAP treated groups compared with the control. As reported [28], the hyperglycemia induction is due to the activation of glycogenolysis process in various organs, in addition to liver gluconeogenesis. Further, the lipid profiles showed a significant increase in cholesterol and triglyceride levels in MAP treated groups compared with control. This can be explained MAP-induced the breakdown of lipids in adipose tissues, resulting

in body weight decrease [29; 24]. Furthermore, the liver enzymatic activity of transaminases (ALT, AST) and alkaline phosphatase (PAL) was significantly increased in MAP treated rats compared with controls. This finding was similarly found in some previous studies [28; 27; 30] investigating the toxic effects of other phytosanitary products in rats. The increased enzymatic activity of ASAT and ALAT explains the liver tissue alterations [31]. However, the marked increase in PAL, a ubiquitous enzyme in liver, bile ducts, kidney, bone, and placenta, indicates the possibility of intrahepatic bile duct obstruction, primary biliary cirrhosis, or disorganization of the hepatic architecture (32). On top of that, MAP cause a significant decrease in protein and albumin levels as compared to control group. Accordingly, the hypoproteinaemia was reported in some previous studies (24; 29). This decrease may be caused by the imbalance between the rate of synthesized proteins and the rate of protein degraded in the liver (33). Interestingly, the hypoproteinaemia with simultaneous decrease in albumin level is generally, considered a non-specific indicator of toxicity, and can be caused by several factors, including reduced food intake, chronic liver disease, and renal protein loss (34). The biochemical kidney markers showed an increased levels of urea, creatinine and uric acid in MAP traded groups compared with control. The changes in these parameters defined as the main kidney function indicators (35) are somehow related to an increase in protein catabolism and a decrease in tubular reabsorption, associated with change in glomerular filtration that indicates the resolution of renal failure (36 ; 37). The liver histopathological findings of MAP treated rats have shown several tissue alterations, including cellular necrosis with hepatic degeneration, dilatation of sinusoids with lymphocytic inflammatory infiltrate associated with congestion of centro-lobular veins. Similar histological results, showing severe liver histology alterations accompanied by cellular necrosis have been previously reported (38; 39; 40). In this regard, MAP caused also marked kidney tissue damages characterized by degeneration of the renal tubules, hypertrophy of the glomeruli, vascular congestion and leukocyte infiltration. Alike to our result, previous studies (41; 40) have reported severe kidney histological alterations in pesticides (abamectin; epoxiconazole) treated rats.

CONCLUSION

The study results showed a significant decrease in body weight, and remarkable alterations in haematological profiles and liver and kidney functional markers in high doses of MAP treated rats. These findings were obviously confirmed by the histopathological observations, showing severe liver and kidney tissue damages.

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Received: **18.03.2022**
Accepted: **07.06.2022**

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