



Research Journal of  
**Environmental  
Toxicology**

ISSN 1819-3420



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## Adverse Haematological and Biochemical Effects of Certain Formulated Insecticides in Male Rats

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### ABSTRACT

Pesticides formulations are complex mixtures and the toxicity information on active ingredients alone is not sufficient to evaluate the risk of adverse health effects of commercial pesticides. So the present study was designed to investigate the adverse effects of exposure to formulated chlorpyrifos-ethyl (9.60 mg kg<sup>-1</sup> b.wt.), chlorpyrifos-methyl (300 mg kg<sup>-1</sup> b.wt.) and methomyl (1.70 mg kg<sup>-1</sup> b.wt.) on some haematological and biochemical parameters of male rats given repetitive oral doses for 90 consecutive days. There was significant decrease in body weight gain of chlorpyrifos-ethyl, chlorpyrifos-methyl and methomyl and increase in relative liver and kidney weights of chlorpyrifos-ethyl and chlorpyrifos-methyl treated rats. Chlorpyrifos-methyl caused significant decrease in Hb conc. Haematocrit value (PCV, %) and Red Blood Cells (RBCs) counts, while chlorpyrifos-ethyl and methomyl caused significant decrease in PCV% and White Blood Cells (WBCs) counts. All of the tested insecticides increased significantly serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) activities and decreased significantly the total protein level. In addition, the tested insecticides caused significant increase in serum uric acid and creatinine. We can conclude that both technical and formulated methomyl and chlorpyrifos-ethyl and its methyl analogues caused significant alteration on hematological and biochemical parameter of male rats. The effects of commercial form of tested insecticides were more pronounced than its technical form.

**Key words:** Haematological, biochemical, uric acid, creatinine, organophosphorus, carbamate, rats, repetitive doses

### INTRODUCTION

Organophosphorus (OPs) and carbamate insecticides have made valuable contribution to human health by increasing food and fiber production and by reducing occurrence of vector-borne diseases (Blindauer *et al.*, 1999). The long-term application of these pesticides has resulted in residues accumulating in soil, water and in different environmental components; thereby posing a serious threat to public health in Egypt (Selim and El-Sebae, 1995). According to World Health Organization report every year, 3 million serious poisonings cases with insecticides occur worldwide and of these approximately 220,000 die (WHO, 1997).

In acute toxicity, the main mechanism of toxicity of OPs and carbamate is binding to the enzyme acetylcholinesterase and inhibiting its activity that results in accumulation and prolonged effect of acetylcholine and consequently follows with acute muscarinic and nicotinic effects

(Ecobichon, 1996). Unfortunately, while the acute toxicity of most pesticides is well-documented (Ecobichon *et al.*, 1990), information on chronic human illness resulting from pesticide exposure is not as sound (Wilkinson, 1990).

In fact, pesticides formulations are complex mixtures and the toxicity information on active ingredients alone is not sufficient to evaluate the risk of adverse health effects of commercial pesticides (Mansour and Mossa, 2005). Consequently, World Health Organization emphasized the necessity of evaluating toxic hazard of the formulated pesticides (WHO, 1991). Therefore, this study was conducted to evaluate the effect of subchronic exposure to formulated chlorpyrifos-methyl, chlorpyrifos-ethyl and methomyl on blood profile and some biochemical parameters of male rats.

## **MATERIALS AND METHODS**

**Chemicals:** Chlorpyrifos-ethyl (Dursban® 48% EC; O,O-diethyl-O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate) and methomyl (Lannate® 90%WP; S-methyl-N-(methyl carbamoyl oxy-thioacetimidate) were supplied from Kafr El-Zayat Pesticides and Chemicals Company, Egypt. Chlorpyrifos-methyl (Reldan® 50% EC; O,O-dimethyl-O-(3,5,6-trichloro-2-pyridinyl phosphorothioate) was supplied by National Agricultural Chemicals Company, Egypt. All other chemicals were of reagent grades and obtained from the local scientific distributors in Egypt.

**Animals, groups and treatments:** Male Wistar rats (weighting 100-120 g) purchased from Animal Health Research Center, Cairo, Egypt. Animals received human care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals." Animals were housed in clean plastic cages with free access to food (standard pellet diet) and tap water *ad libitum*, under standardized housing conditions (12 h light/dark cycle, temperature was 22±1°C and a minimum relative humidity of 40%) in the laboratory animal room. After one week of adaptation to laboratory conditions, the animals randomly divided into four groups each comprising of six animals, as follows: first group (chlorpyrifos-methyl), second group (chlorpyrifos-ethyl), third group (methomyl) and fourth group (control).

Tested insecticides were daily freshly prepared, adjusted weekly for body weight changes and administered orally for 90 consecutive days. All treatments were administered at a dose equal to 0.1 LD<sub>50</sub>, as reported by Tomlin (2004), chlorpyrifos-ethyl (9.60 mg a.i. kg<sup>-1</sup> b.wt.), chlorpyrifos-methyl (300 mg a.i. kg<sup>-1</sup> b.wt.) and methomyl (1.70 mg a.i. kg<sup>-1</sup> b.wt.). The control group received an equivalent volume of distilled water (0.5 mL rat<sup>-1</sup>).

**Blood collection and relative organs weights:** In all groups, body weights were weekly recorded. At the end of exposure period, blood samples drawn from all rats under ether anesthesia and collected in EDTA-tubes for haematological studies and normal glass tubes to separate the sera for biochemical studies. Then, within 20 min of blood collection, the sera samples were drawn from blood after centrifugation at 3500 rpm (600 g) for 10 min at 4°C, using Universal 32 R centrifuge (Hettich-Zentrifugen GmbH, Tuttlingen, Germany). The sera was kept in a deep freezer (-20°C) until analyzed.

After blood collection, the rats were sacrificed by cervical dislocation. Liver and kidney of rats were removed and weighted. Then, the relative organs weights were calculated.

**Measurement of blood constituents:** Red Blood Cells (RBC's) and White Blood Cells (WBC's) were counted according to the methods of Britton (1963) and Seiverd (1964). Haemoglobin (Hb)

measurement was carried out according to Wintrobe method (Wintrobe, 1965). Haematocrit value (PCV) was determined using microhaematocrit centrifuge Model SH120.

**Determination of liver and kidney biomarkers:** Serum ALT and AST activities were measured as described by Reitman and Frankel (1957) accordance with manufacturers' instructions. Total protein was determined by the method described by Henry (1964), creatinine determination was done according to Henry (1974) and uric acid was determined by the methods of Barham and Trinder (1972) and Fossati *et al.* (1980) using Boehringer Mannheim Gmbh Diagnostic Kits.

**Spectrophotometric measurements:** The Spectrophotometric measurements were performed by using a Jenway, UK, 6305 UV/Vis spectrophotometer.

**Statistical analysis:** The data were analyzed by using SPSS (version 11.0) for Windows and expressed as means $\pm$ SE. Paired samples t-test was used to compare between the data of the control and those of treatments. The level of significance was 0.05 and 0.01.

## RESULTS

Repeated oral administration of chlorpyrifos, chlorpyrifos-methyl and methomyl at 9.6, 300 and 1.7 mg kg day<sup>-1</sup> did not produce any signs of toxicity and mortality during 90 days exposure. However, there was significant decrease of body weight gain of chlorpyrifos, chlorpyrifos-methyl and methomyl treated rats (Fig. 1). The body weight recorded 186.26 g in the control group and decreased to 175.80, 172.40 and 162.85 g in CPF-methyl, CPF-ethyl and methomyl treated groups, respectively. Also, the relative organ weights of liver and kidney were significantly increased in chlorpyrifos and chlorpyrifos-methyl treated rats groups compared to the control (Fig. 2). The relative liver and kidney weights accounted 2.79 and 0.63% in control and elevated to 3.42, 3.78 and 2.81% of liver and 0.77, 0.78 and 0.64% of kidney in CPF-methyl, CPF-ethyl and methomyl treated groups, respectively.

**Blood profile:** Results of Hb, PCV, RBC's and WBC's are shown in Table 1. Except the treatments of chlorpyrifos-methyl, the rest of the treatments caused insignificant decrease of haemoglobin (Hb) and the decrease in case of chlorpyrifos-methyl accounted to 13.1 g dL<sup>-1</sup> in

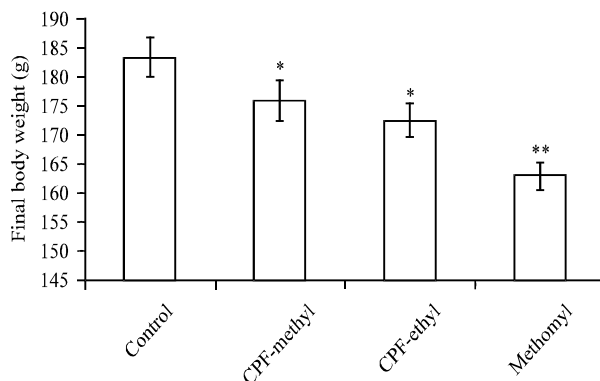


Fig. 1: Body weights of rats exposed to tested insecticides for 90 consecutive days, Each value is a means $\pm$ SE; n = 6, Statistical difference from the control: \*Significant at p<0.05 and \*\*Highly significant at p<0.01, CPF: Chlorpyrifos

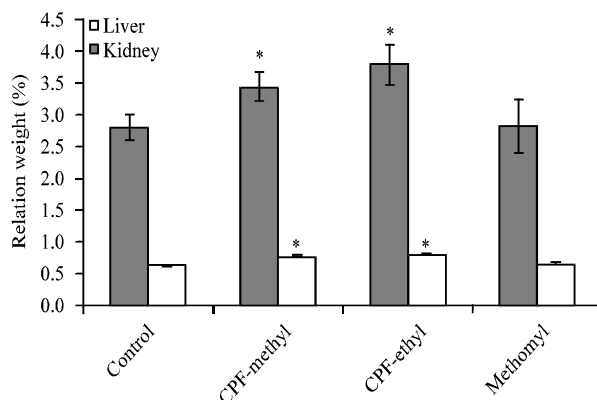


Fig. 2: Relative liver and kidney weights of rats exposed to tested insecticides for 90 consecutive days, Each value is a means $\pm$ SE; n = 6, Statistical difference from the control: \*Significant at  $p < 0.05$  and \*\*Highly significant at  $p < 0.01$ . Relative weight (%) = (organ weight/body weight) $\times$ 100, CPF: Chlorpyrifos

Table 1: Blood profile of rats exposed to test formulated insecticides for 90 consecutive days

Treatments	Hb (g dL <sup>-1</sup> )	PCV (%)	RCB's ( $\times 10^6$ /mm <sup>3</sup> )	WBC's ( $\times 10^3$ /mm <sup>3</sup> )
Control	22.70 $\pm$ 0.20	48.66 $\pm$ 2.30	3.97 $\pm$ 0.20	15.80 $\pm$ 0.10
Chlorpyrifos-methyl	13.10 $\pm$ 1.10**	25.00 $\pm$ 1.70**	2.54 $\pm$ 1.30**	15.00 $\pm$ 1.08
Chlorpyrifos-ethyl	20.80 $\pm$ 1.50	35.00 $\pm$ 2.50**	3.55 $\pm$ 0.40	12.20 $\pm$ 0.31*
Methomyl	21.00 $\pm$ 2.40	30.00 $\pm$ 1.54**	3.93 $\pm$ 0.41	14.10 $\pm$ 0.30*

Each value is a Mean $\pm$ SE, n = 6; Statistical difference from the control: \*Significant at  $p \leq 0.05$  and \*\*Highly significant at  $p \leq 0.01$ . Hb: Hemoglobin; RBC's: Red blood cells; WBC's: White blood cells and PVC: Haematocrit value

Table 2: AST and ALT activities and total protein and glucose level in the sera of rats exposed to test formulated insecticides for 90 consecutive days

Treatments	AST (U L <sup>-1</sup> )	ALT (U L <sup>-1</sup> )	Total protein (mg dL <sup>-1</sup> )
Control 21.3 $\pm$ 1.91	25.5 $\pm$ 3.17	8.39 $\pm$ 0.81	
Chlorpyrifos-methyl	140.6 $\pm$ 2.82**	98.7 $\pm$ 4.25**	6.53 $\pm$ 0.29*
Chlorpyrifos-ethyl	200.6 $\pm$ 2.84**	104.0 $\pm$ 3.81**	6.34 $\pm$ 0.17*
Methomyl	69.2 $\pm$ 3.40*	75.4 $\pm$ 2.69*	6.38 $\pm$ 0.56*

Each value is a Mean $\pm$ SE, n = 6; Statistical difference from the control: \*Significant at  $p \leq 0.05$  and \*\*Highly significant at  $p \leq 0.01$ . Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

comparison to control value, 22.7 g dL<sup>-1</sup>, which was statistically highly significant ( $p < 0.01$ ). Packed Cell Value (PCV) is a parameter for determination of the volume of red blood cell. All formulated insecticides caused significant decrease ( $p < 0.01$ ) of the PCV %, chlorpyrifos-methyl was more effective than other insecticides and showed value accounted to 25.00% compared to control value, 48.66%. On the other hand, RBC's counts was statistically decrease ( $p < 0.01$ ) after treatment with chlorpyrifos-methyl and accounted to 2.54 compared to control value  $3.97 \times 10^6$  mm. In contrast, chlorpyrifos-ethyl and methomyl caused decrease in WBC's counts accounted to 12.20 $\pm$ 0.31 and 14.10 compared to control value  $15.80 \times 10^3$  mm which was statistically significant ( $p < 0.05$ ).

**Liver and kidney biomarkers:** The results of serum biochemical parameters of male rats orally administered the tested formulated pesticides for 90 days are shown in Table 2. Serum biochemical

Table 3: Uric acid and creatinine concentration in the sera of rats exposed to test formulated insecticides for 90 consecutive days

Treatments	Uric acid (mg dL <sup>-1</sup> )	Creatinine (g dL <sup>-1</sup> )
Control	4.06±0.34	1.51±0.02
Chlorpyrifos-methyl	6.55±0.32*	1.94±0.02*
Chlorpyrifos-ethyl	3.98±0.16	2.26±0.05**
Methomyl	7.41±0.24**	2.16±0.06**

Each value is a Mean±SE, n = 6, Statistical difference from the control: \*Significant at p≤0.05 and \*\*Highly significant at p≤0.01

parameters, AST and ALT activities were significantly increased than that of control rats and the formulated OP's insecticides seemed to induce higher elevation of AST and ALT activities than carbamate insecticide, methomyl. On the other hand, all of the tested insecticides induced significant decreases in serum total protein as compared with the untreated group.

As shown in Table 3, chlorpyrifos-methyl (6.55 mg dL<sup>-1</sup>) and methomyl (7.41 mg dL<sup>-1</sup>) caused significant elevation of serum uric acid as compared to the control (4.06 mg dL<sup>-1</sup>). In addition, all of the tested insecticides induced significant increases in sera creatinine as compared with the untreated rats.

## DISCUSSION

The present study investigated the adverse effects of exposure to formulated chlorpyrifos-ethyl (9.60 mg kg<sup>-1</sup> b.wt.), chlorpyrifos-methyl (300 mg kg<sup>-1</sup> b.wt.) and methomyl (1.70 mg kg<sup>-1</sup> b.wt.) on some haematological and biochemical parameters of male rats given repetitive oral doses for 90 consecutive days.

Changes in the body weight after insecticide dosing was used as a valuable index of insecticide-related organ damage (Lu, 1996; Mansour and Mossa, 2010a; Mossa *et al.*, 2011). In the present study, results revealed that all of the tested insecticides caused significant decrease in body weights of treated rats and increase in the relative weight of liver and kidney. The reduction in body weight gains may be due to the overall increased degradation of lipids and proteins as a result of the direct effects of anti-cholinesterase compound (Goel *et al.*, 2005; Mansour and Mossa, 2011; Mossa *et al.*, 2011). Other investigations have reported the reduction in body weight and change in relative organs weights in rats (Woolliams *et al.*, 1983; Mansour *et al.*, 2001; Mossa *et al.*, 2011) and mice (Ambali *et al.*, 2007) after exposure to anti-cholinesterase insecticides.

In fact, haemoglobin concentration and haematocrit values are directly correlating with RBC's count (El-Bakary *et al.*, 1995). This is due to the synergistic link among these blood parameters in all vertebrates. This close correlation between erythrocyte count, haemoglobin concentration and haematocrit value was also reported for other vertebrates including man (Harris, 1972). In the present study, chlorpyrifos-methyl caused significant decrease in haemoglobin (Hb) concentration. Packed cell value (PCV%) is a parameter for determination of the volume of red blood cell. All formulated insecticides caused significant decrease (p<0.01) in the PCV%, chlorpyrifos-methyl was more effective than other insecticides. RBC's counts was statistically decrease (p<0.01) after treatment with chlorpyrifos-methyl. In contrast, chlorpyrifos-ethyl and methomyl caused decrease in WBC's counts and WBC's was accounted 12.20±0.31 and 14.10 compared to control value (15.80), which was statistically significant (p<0.05). Previous studies found that the direct effect of pesticides is a reduction in the total number of erythrocytes, PCV and Hb content (El-Sahhaf, 1995; Saxena and Saxena, 1997; El-Gendy *et al.*, 1999; Khalaf-Allah, 1999; Yousef *et al.*, 1999; Mossa, 2004). It was thought that these changes were due to an increase rate of breakdown of red cells and/or the toxic effect of pesticides on bone marrow. The increase of WBC's may be due to the activation of the animal's defense mechanism and immune system. Also, the reduction in Hb

content may be due to increased rate of breakdown of red cells and/or reduction in the rate of formation of RBC's (Mossa, 2004). Shakoori *et al.* (1990) suggested that the decrease in RBC is either indicative of excessive damage to erythrocytes or inhibition of erythrocyte formation in rabbits. In this work, results agree in most cases with the results of several authors. Shakoori *et al.* (1990) found decrease in erythrocytic, leukocytic counts; PCV and Hb content in the blood of bifenthrin-treated rabbits.

Liver is the first organ to face any foreign molecule that is carried through portal circulation and it is subjected to most damage. In addition, transaminase (AST and ALT) are important enzymes in the biological processes. They play a role in amino acids catabolism and biosynthesis. Consequently, they are considered as specific indicators for liver damage (Harper, 1979) and responsible for detoxification processes, metabolism and biosynthesis of energetic macromolecules for different essential functions (Aly *et al.*, 1997). The present results showed a significant increase in the activities of both AST and ALT in the serum of treated rats. Hayes *et al.* (1989) reported that one of the most indicators for liver damage and function is increase in the activities of serum transaminase (AST and ALT) in the serum. This increasing may be indicative of initial cell injury occurring in advance of gross hepatic pathology, since not only distinct cellular damage but also any condition leading to changes in membrane permeability also causes a generalized release of enzymes from the cell (De Bruin, 1979). Several studies have showed that the activities of transaminases were increased in human and animals after exposure to pesticides (Khalaf-Allah, 1999; Abbassy *et al.*, 2000; Mossa, 2004; Mansour and Mossa, 2011; Mossa *et al.*, 2011).

Results revealed that the tested insecticides caused a significant decrease in total protein and highly significant increase in creatinine in the sera of rats compared to control. On the other hand, chlorpyrifos-methyl and methomyl caused significant increase in serum uric acid. The protein content in different organs was affected as a result of exposure to different insecticides (Enan *et al.*, 1982; Nabila *et al.*, 1990; El-Bakary, 1993; Khan *et al.*, 2003; Mossa, 2004; Mansour and Mossa, 2010a, b; 2011; Mossa *et al.*, 2011). The decrease in protein content might be due to the imbalance between the rate of protein synthesis and the rate of its degradation in the liver. Rodwell (1979) reported that an elevated level of urea in blood is correlated with an increase protein catabolism in the mammalian body. It may also result due to a more efficient conversion of ammonia to urea as a result of increased synthesis of enzyme involved in urea production (Rodwell, 1979; El-Sebae *et al.*, 1981). Other investigations showed an increase of urea and creatinine in the serum of chicks and rats-treated with acute and chronic doses of 2,4-D and cypermethrin (Charles and Leeming, 1998; Yousef *et al.*, 1999). Creatinine is a metabolite of creatine and is excreted completely in urine via glomerular filtration. An elevation of its level in the blood is thus an indication of impaired kidney function (Lu, 1996).

The effects of chlorpyrifos-ethyl and its methyl analogues on hematological and biochemical parameter revealed that these compounds caused significant alteration in blood picture, liver and kidney biomarkers in treated rats. The effect of chlorpyrifos-ethyl was more pronounced than its methyl analogues in its commercial form. Also, chlorpyrifos-ethyl was most toxic (acute oral LD<sub>50</sub> for rats 135-163 mg kg<sup>-1</sup>) and chlorpyrifos-methyl (acute oral LD<sub>50</sub> for rats >3000). The two OP insecticides contain the same structure except the substitution of ethyl groups in chlorpyrifos by methyl groups in chlorpyrifos-methyl, which was less in its mammalian toxicity than chlorpyrifos. This substitution may affect the intrinsic toxicity and/or sensitivity of the structure to the metabolic systems in the treated rats (Mossa, 2004; Abbassy *et al.*, 2005).

## CONCLUSION

We can conclude that both technical and formulated methomyl and chlorpyrifos-ethyl and its methyl analogues caused significant alteration on hematological and biochemical parameter of male rats. The effects of commercial form of tested insecticides were more pronounced than its technical form.

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