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## Haemato-biochemical Effects of Formulated and Technical Cypermethrin and Deltamethrin Insecticides in Male Rats

<sup>1</sup>Moustafa A. Abbassy and <sup>2</sup>Abdel-Tawab H. Mossa

<sup>1</sup>Department of Plant Protection, Faculty of Agriculture Damanhour, Damanhour University, Egypt

<sup>2</sup>Environmental Toxicology Research Unit (ETRU), Department of Pesticide Chemistry, National Research Centre, Cairo, Egypt

*Corresponding Author: Abdel-Tawab H. Mossa, Environmental Toxicology Research Unit (ETRU), Department of Pesticide Chemistry, National Research Centre, Cairo, Egypt*

### ABSTRACT

Pesticide 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 work was conducted to study the haemato-biochemical effects of technical and formulated cypermethrin (25.0 mg kg<sup>-1</sup> b.wt.) and deltamethrin (1.70 mg kg<sup>-1</sup> b.wt.), in male rats given repetitive oral doses for 90 consecutive days. There was high significant decrease ( $p \leq 0.01$ ) in body weight gain of cypermethrin and significant decrease ( $p \leq 0.05$ ) in deltamethrin treated rats. The relative liver and kidney weights were significantly change in the treatments of formulated and technical cypermethrin and deltamethrin compared to the control. Deltamethrin as technical or formulated form caused significant changes ( $p \leq 0.01$ ) in haemoglobin, packed cell value and Red Blood Cell (RBC), while formulated and technical cypermethrin caused significant decrease ( $p \leq 0.05$ ) in PCV % and formulated cypermethrin induced significant decrease ( $p \leq 0.01$ ) in White Blood Cell (WBC) compared to control value. Treatments with formulated and technical cypermethrin and deltamethrin caused significant increase ( $p \leq 0.01$ ) in serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) activities and formulated cypermethrin seemed to induce higher AST elevation (200.67 IU L<sup>-1</sup>) and formulated deltamethrin induce higher ALT elevation (105.07 IU L<sup>-1</sup>) as compared with the untreated group (21.30 and 25.50 IU L<sup>-1</sup>, respectively). Technical cypermethrin and deltamethrin caused highly significant ( $p \leq 0.01$ ) decreased in serum glucose. On the other hand all of the tested insecticides induced significant decreases ( $p \leq 0.05$ ) in serum total protein and increase ( $p \leq 0.05-0.01$ ) in creatinine and uric acid concentrations. The partial differences of hematological and biochemical effects obtained with pure and commercial deltamethrin and cypermethrin indicate that commercial formulations may contain additional hazardous compounds. Therefore, it is important in assessing the real human hazard from pesticides to investigate not only the active principle but also the commercial formulations used in agriculture.

**Key words:** Haematological, biochemical changes, liver-serum enzymes, uric acid, creatinine, pyrethroids, rats, repetitive doses

### INTRODUCTION

Pesticides are used extensively all-over the world in plant protection. These pesticides have made valuable contributions to human health by increasing food and fiber production and by reducing the occurrence of vector-borne diseases (Blindauer *et al.*, 1999). However, 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 poisoning cases with insecticides occur worldwide and of these approximately 220,000 die (WHO, 1997). 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). It has been estimated that occupational exposure accounts for 4% of all human cancers (Doll and Peto, 1981).

With regulatory limitations on the use of cholinesterase-inhibiting insecticides, synthetic pyrethroids have become increasingly important in both agricultural and structural pest control (US EPA, 1996). These insecticides are known to possess high activity against a broad spectrum of insect pests, low acute toxicity in mammals and lack of persistence in the environment (Papadopoulou-Markidou, 1983; Zerba, 1988; Vijveberg and Van den Bercken, 1990). For these reasons, synthetic pyrethroid insecticides are extensively used in agriculture and in household products.

The public health effects of pesticides cannot be denied. However, the undesired effects of chemical pesticides have been recognized as a serious public health concern during the past decades (Mossa and Abbassy, 2012), the pesticides selected in this study are two pyrethroids: cypermethrin and deltamethrin insecticides. These insecticides are highly effective against a broad spectrum of insects and are widely used in agriculture and public health programs. Since, human exposure to pesticides occurs not only to active principles but also to all chemicals present in a commercial formulation, we tested both the pure compounds and their commercial formulations.

The hepatotoxicity of these classes of insecticides is still controversial (Tomei *et al.*, 1998). For this reason, the present work conducted to study the haemato-biochemical effects of technical and formulated cypermethrin and deltamethrin in male rats.

## MATERIALS AND METHODS

**Chemicals:** Cypermethrin [95.1%; (RS)- $\alpha$ -cyano-3-phenoxybenzyl (1RS, 3RS; 1RS, 3RS)-3-(2, 2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylate] obtained from Zhongshan Sino-agro chemical co Ltd, China and Sparkle<sup>®</sup> (25% EC) from Al-Help Pesticides and Chemicals Company, Egypt. Deltamethrin [98.7%; (S)- $\alpha$ -cyano-3-phenoxybenzyl (1R, 3R)-3-(2, 2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylate] obtained from Jiangsu Yangnong Chemical Co., Ltd, India and K-Othrin<sup>®</sup> (2.5% WP) from Kafr El-Zayat Pesticides and Chemicals Company, Egypt. Kits of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total protein, creatinine and uric acid were obtained from Boehringer Mannheim, GmbH, Diagnostica, Germany.

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 humane 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 five groups each comprising of six

animals, as follows: first group (technical cypermethrin), second group (formulated cypermethrin), third group (technical deltamethrin), fourth group (formulated deltamethrin) and fifth 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), cypermethrin (25.0 mg a.i. kg<sup>-1</sup> b.wt.) and deltamethrin (1.70 mg a.i. kg<sup>-1</sup> b.wt.). The control group received an equivalent volume of corn oil (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 were 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 as:

$$\text{Relative weight} = \frac{\text{Organ weight}}{\text{Body weight}} \times 100$$

**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), respectively.

**Spectrophotometric measurements:** The Spectrophotometric measurements were performed by using a Jenway, UK, 6305 UV/Vis spectrophotometer at 546 nm.

**Statistical analysis:** The data were analyzed by using SPSS (version 11.0) for Windows and expressed as Mean±SE. Paired samples t-test was used to compare between the data of the control and those of treatments.

## RESULTS

**Body weight and relative organ weights:** Oral administration of technical and formulated cypermethrin and deltamethrin at 25.0 and 1.70 mg a.i. kg<sup>-1</sup> day<sup>-1</sup> did not produce any signs of toxicity and mortality during 90 days exposure. In contrast, there was high significant decrease (p≤0.01) of body weight gain of cypermethrin and significant decrease (p≤0.05) of deltamethrin treated rats (Fig. 1). Body weights were recorded 83.26 g in control and decrease to 44.65, 55.74,

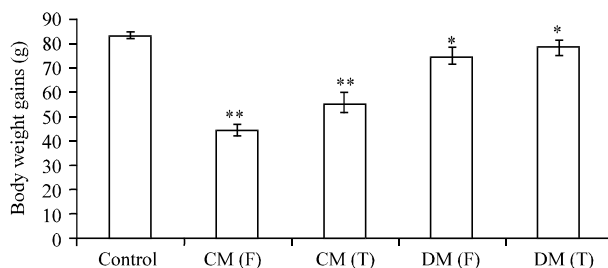


Fig. 1: Body weight gains of rats exposed to cypermethrin (CM) and deltamethrin (DM) for 90 consecutive days, Each value is a Mean±SE, n = 6, \*Significant at p≤0.05, \*\*Highly significant at p≤0.01 when compared to control, F: Formulated, T: Technical

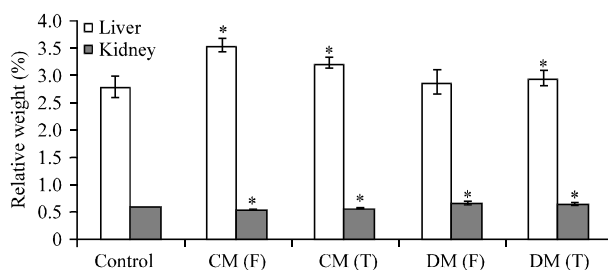


Fig. 2: Relative liver and kidney weights of rats exposed to cypermethrin (CM) and deltamethrin (DM) for 90 consecutive days, Each value is a Mean±SE, n = 6, \*Significant at p≤0.05 when compared with control, F: Formulated, T: Technical

Table 1: Blood profile of rats exposed to cypermethrin and deltamethrin for 90 consecutive days

Treatments	Hb (g dL <sup>-1</sup> )	PCV (%)	RCB (×10 <sup>6</sup> mm <sup>-3</sup> )	WBC (×10 <sup>3</sup> mm <sup>-3</sup> )
Control	22.70±1.20	48.66±2.30	3.97±0.20	15.80±0.10
Cypermethrin (F)	21.87±1.90	42.00±1.10*	3.57±0.19	11.96±0.27**
Cypermethrin (T)	20.21±1.75	40.00±1.15*	3.54±0.31	15.19±0.32
Deltamethrin (F)	17.57±1.12**	38.00±1.50**	2.48±0.16**	16.36±0.26
Deltamethrin (T)	12.74±0.95**	39.00±0.57**	5.26±0.13**	15.96±0.20

Each value is a Mean±SE, n = 6; Statistical difference from the control: \*Significant at p≤0.05, \*\*Highly significant at p≤0.01. F: Formulated, T: Technical, Hb: Hemoglobin, RBC: Red blood cells, WBC: White blood cells, PCV: Haematocrit value

74.62 and 78.24 g of formulated and technical cypermethrin and deltamethrin-treatments, respectively. As shown in Fig. 2, the relative liver weights were significantly increase (p≤0.05) in the treatments of formulated and technical cypermethrin (3.55 and 3.22%) and deltamethrin (2.87 and 2.95%) compared to the control (2.79%). In contrast, significant decrease in relative kidney weights were recorded in treatment of formulated and technical cypermethrin (0.56 and 0.59%) and significant increase in the treatment of formulated and technical deltamethrin (0.68 and 0.67%) as compared to the corresponding control (0.63%).

**Hematotoxicity:** The hematotoxicity of technical and formulated cypermethrin and deltamethrin are shown in Table 1. The treatments of deltamethrin as technical or formulated form caused significant changes (p≤0.01) in haemoglobin (17.52 and 12.74 g dL<sup>-1</sup>), packed cell value (38 and 39%) and RBC's (2.48 and 5.26×10<sup>6</sup> mm<sup>-3</sup>) in comparison to control values (22.7 g dL<sup>-1</sup>, 48.66% and 3.97×10<sup>6</sup> mm<sup>-3</sup>, respectively). In the contrast, formulated and technical cypermethrin caused

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

Treatments	AST (IU L <sup>-1</sup> )	ALT (IU L <sup>-1</sup> )	Total protein (mg dL <sup>-1</sup> )	Glucose (mg dL <sup>-1</sup> )
Control	21.30±1.91	25.50±3.17	8.39±0.81	66.50±1.20
Cypermethrin (F)	200.67±2.89**	64.26±2.80**	6.32±0.20*	33.94±1.17**
Cypermethrin (T)	199.56±0.50**	61.45±1.15**	6.68±0.34*	25.07±0.33**
Deltamethrin (F)	72.70±1.70**	105.07±3.98**	6.26±0.18*	49.41±2.36**
Deltamethrin (T)	70.96±2.13**	101.16±1.35**	6.56±0.05*	39.30±3.46**

Each value is a Mean±SE, n = 6, \*\*\*Significant at p<0.05 and highly significant at p<0.01 when compared with control, respectively, F: Formulated, T: Technical, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

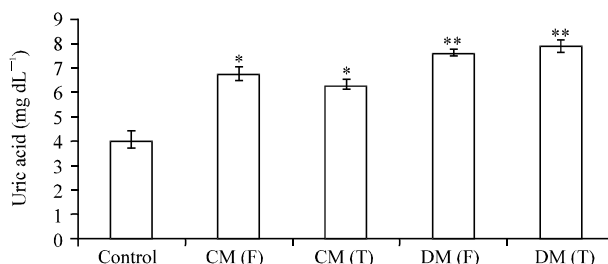


Fig. 3: Uric acid concentration in the sera of rats exposed to cypermethrin (CM) and deltamethrin (DM) for 90 consecutive days. Each value is a Mean±SE, n = 6, \*\*\*Significant at p<0.05 and highly significant at p<0.01 when compared with control, respectively, F: Formulated, T: Technical

significant decrease (p<0.05) of the PCV% and showed value accounted to 42.0 and 40.0% compared to control value, 48.66%. While, formulated cypermethrin induced significant decrease (p<0.01) in WBC's counts and accounted to 11.63×10<sup>3</sup> mm<sup>-3</sup> compared to control value 15.80×10<sup>3</sup> mm<sup>-3</sup>.

**Liver and kidney dysfunction markers:** The effect of formulated and technical cypermethrin and deltamethrin on liver biomarkers e.g., AST, ALT, total protein and blood glucose are shown in Table 2. Treatments with formulated and technical cypermethrin and deltamethrin caused significant increase (p<0.01) in serum AST and ALT activities and formulated cypermethrin insecticide seemed to induce higher AST elevation (200.67 IU L<sup>-1</sup>), while formulated deltamethrin induce higher ALT elevation (105.07 IU L<sup>-1</sup>) as compared with the untreated group (21.30 and 25.50 IU L<sup>-1</sup>, respectively). Results showed that technical cypermethrin and deltamethrin caused highly significant (p<0.01) decreased in serum glucose as compared with the untreated group. On the other hand all of the tested insecticides induced significant decreases (p<0.05) in serum total protein as compared with the untreated group. The level of total protein accounted 8.39 mg dL<sup>-1</sup> and decreased to 6.32, 6.68, 6.26 and 6.56 mg dL<sup>-1</sup> of formulated and technical cypermethrin and deltamethrin, respectively.

Deltamethrin treatments caused highly significant increases (p<0.01) in serum uric acid concentration while cypermethrin treatments caused significant increases (p<0.05) compared to the corresponding control group (Fig. 3). Uric acid levels were recorded 6.04 mg dL<sup>-1</sup> in control and increase to 6.78, 6.33, 7.65 and 7.90 mg dL<sup>-1</sup> of formulated and technical cypermethrin and deltamethrin treatments, respectively.

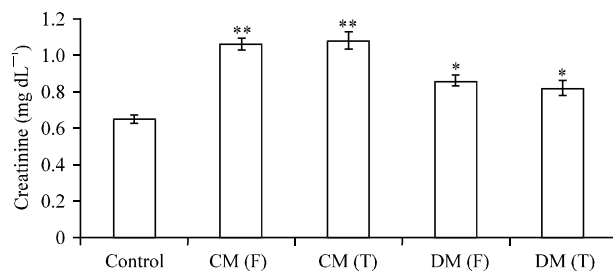


Fig. 4: Creatinine concentration in the sera of rats exposed to cypermethrin (CM) and deltamethrin (DM) for 90 consecutive days. Each value is a Mean $\pm$ SE, n = 6, \*\*\*Significant at  $p \leq 0.05$  and highly significant at  $p \leq 0.01$  when compared with control, respectively, F: Formulated, T: Technical

Figure 4 show the effect of the tested insecticides on creatinine concentration in serum of rats given repetitive doses ( $0.1 LD_{50}$ ) for 90 consecutive days. Formulated and technical cypermethrin induced highly significant increases ( $p \leq 0.01$ ) in serum creatinine, while formulated and technical deltamethrin induced significant increases ( $p \leq 0.05$ ) as compared with the untreated group. Creatinine concentration was accounted  $0.65 \text{ mg dL}^{-1}$  in control group and increased to  $1.06$ ,  $1.08$ ,  $0.86$  and  $0.82 \text{ mg dL}^{-1}$  of formulated and technical cypermethrin and deltamethrin treatments, respectively.

## DISCUSSION

The present study was designed to investigate the adverse effects of exposure to cypermethrin and deltamethrin insecticides on some haematological and biochemical parameters of male rats given repetitive oral doses for 90 consecutive days. In the present study, significant decrease in body weight gain at end of the experimental period following administration of technical and formulated cypermethrin and deltamethrin in rat has been observed. It may be attributed to the effect of insecticides on gastrointestinal tract resulting in decreased appetite and absorption of nutrients from gut (Venkateshwarlu *et al.*, 1997) or might be due to direct toxicity of cypermethrin and deltamethrin insecticides (Sankar *et al.*, 2012). The increase in the kidney size after exposure to toxins has also been reported by Kumar *et al.* (1997). The probable reason for the increase in the weight of kidneys may be congestion of vessels and lymphocytic infiltration (Inayat *et al.*, 2007). Other investigations have reported the reduction in body weight and change in relative organs weights in cypermethrin-treated rats (Hussain *et al.*, 2009; Sangha *et al.*, 2011) and in rabbits (Lakkawar *et al.*, 2004). Lambda cyhalothrin administered orally to rats has also resulted in reduced body weight gain in both male and female rats (Ratnasooriya *et al.*, 2002).

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, significant decrease in Haemoglobin (Hb) concentration, PCV % and RBC's count at end of the experimental period following administration of technical and formulated cypermethrin and deltamethrin in rat has been observed. 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. 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, 1997; El-Gendy *et al.*, 1999; Khalaf-Allah, 1999; Yousef *et al.*, 1999; Mossa, 2004; Mossa and Abbassy, 2012). 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. Our results revealed that; formulated cypermethrin induced significant decrease ( $p \leq 0.01$ ) in WBC's counts and accounted to  $11.63 \times 10^8 \text{ mm}^{-3}$  compared to control value  $15.80 \times 10^8 \text{ mm}^{-3}$ . The increase of WBC's may be due to the activation of the animal's defense mechanism and immune system. In this study, 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. Transaminases (AST and ALT) are important enzymes in the biological processes. They play a role in amino acids catabolism and biosynthesis. Consequently, they are considering 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). These enzymes were secreted to blood in hepatocellular injury and their levels increase. Changes in these enzymes levels might differ dependent on exposure time and dose. The noticed increase in the levels of aminotransferase (ALT and AST) and decrease in the levels of total protein in the serum are the major diagnostic symptoms of liver diseases. The present results showed a significant increase in the activities of both AST and ALT in the serum of treated rats. The increase in the activities of these enzymes in serum is indicative for liver damage and thus causes alteration in liver function. Several studies have showed that the activities of transaminases were increased in human and animals after exposure to pesticides (Khalaf-Allah, 1999; Mossa, 2004; Mansour and Mossa, 2011; Mossa *et al.*, 2011; Mossa and Abbassy, 2012).

Results showed that technical cypermethrin and deltamethrin caused highly significant ( $p \leq 0.01$ ) decreased in serum glucose and significant decreases ( $p \leq 0.05$ ) in serum total protein as compared with the untreated group. 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; Mossa and Abbassy, 2012). 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.

In the present study, deltamethrin and cypermethrin treatments caused significant increases in serum uric acid and creatinine concentrations in treated rats. 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).

In general, results of our study revealed that deltamethrin was more toxic than cypermethrin. A structure-activity relationship for synthetic pyrethroids has been shown for their physiological and behavioral effects on rats. It is well established that the two pyrethroids contain the same



alcohol moiety ( $\alpha$ -cyano-3-phenoxybenzyl) but substitution of 3-(2, 2-dichlorovinyl)-2, 2-dimethyl cyclopropane carboxylic acid in structure of cypermethrin by 3-(2, 2-dibromovinyl)-2, 2-dimethyl cyclopropane carboxylic acid gives deltamethrin which was more toxic than cypermethrin. The above mentioned substitution may affect the intrinsic toxicity and/or induced sensitivity of the structure to the metabolic systems in the treated rats (Mossa, 2004; Abbassy *et al.*, 2005; Mossa and Abbassy, 2012).

## CONCLUSION

Formulated and technical deltamethrin and cypermethrin were induced haematological and biochemical changes in male rats. The partial differences of hematological and biochemical effects obtained with pure and commercial deltamethrin and cypermethrin indicate that commercial formulations may contain additional hazardous compounds. Therefore, it is important in assessing the real human hazard from pesticides to investigate not only the active principle but also the commercial formulations used in agriculture.

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