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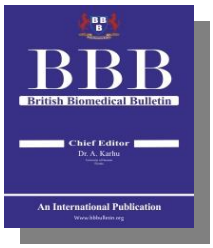

Original

Effects of Profenofos and Chlorpyrifos Pesticides on Oxidative Stress Biomarker, Biochemical Toxicity, DNA and RNA Content of Male Albino Mice

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ABSTRACT

Objective: The present study aimed to evaluate the profenofos and Chlorpyrifos pesticides on oxidative stress biomarker, biochemical toxicity, DNA and RNA content of male Albino mice. **Method:** The animals were divided into three groups of equal number, The control group (1) was orally and daily administered with an equivalent amount of the vehicle (distilled water) for two weeks, the second group was given drinking water with 1.5 mg/kg BW of profenofos during two weeks of oral and daily administration and the third group were orally and daily administered with Chlorpyrifos (1.5 mg /kg BW). At the ends of the experimental period (2 weeks), the mice were sacrificed under diethyl ether anesthesia at fasting state. **Results:** The present results showed that the activities of Superoxide dismutase (SOD), Catalase and glutathione reductase (GR), enzymes in homogenate of snail's tissues were decreased in the tissues of mice treated profenofos and Chlorpyrifos while lipid peroxide (LP) activity increased. Also, the profenofos and Chlorpyrifos pesticide caused a gradual significant reduction of enzyme activities of ALT, AST and ALP and increases in the glucose level and acid phosphatase in serum of male mice Also, the activity of glycolytic (PK, PFK and GPI) and gluconeogenic enzyme activities (F-1, 6-D-Pase) were significantly increased in tissues of treated mice. The change in the intensity number and position of DNA bands resulting from the profenofos and Chlorpyrifos pesticides can be attributed to the fact that herbicides can occur genotoxicity. **Conclusion:** The pollution the water environment by profenofos and pesticide chlorpyrifos, would negatively impact on the metabolism of mice and genetic toxicity products at low concentration and treatment for a long time and demonstrated the risk addicting herbicides to human health.

Introduction

Pesticide application is an important procedure to enhance agricultural output. However, the pesticide use that may contaminate Drainage and Irrigation systems during the planting and control pests activities, and thus negatively affect vital components and is vital for the session polluted water[1,2].

Some pesticides are a continuation of the environment, and can affect pollution of aquatic species and the wild alike[3-5].

The pollutants, especially pesticide, can disturb the aquatic organisms at the cellular, physiological and molecular levels[6]. In spite of studies of the biological impacts of pesticides has increased over the last years, and the results for these products genotoxicity is often incomplete and sometimes conflicting[7].

One of pesticides and profenofos is moderately toxic to the birds and mammals had low toxicity with insecticidal good[8].

Also, it induced programmed cell death and necrosis in cultured lymphocytes in human peripheral blood under the circumstances in the laboratory using the DNA diffusion examination[9,10].

Chlorpyrifos is an organophosphate insecticide. Clean chlorpyrifos composed of white or colorless crystals. It has a skunk odor, like rotten eggs or garlic.

Chlorpyrifos is used to control many different types of pests, including termites, mosquitoes, and worms. Chlorpyrifos has been registered as a pesticide in 1965 and the United States Environmental Protection Agency (U.S. EPA) re-registered it in 2006.

Using only in enclosed places of chlorpyrifos is legal in containers with the bait treatment[11]. Chlorpyrifos (CPF), and organic phosphate applied widely in agriculture and aquaculture, pays oxidative stress due to the generation free radicals and changes in antioxidant defense system[12]. Organophosphate pesticide represents one of the world's most commonly used agrochemical. Consequently, many of its residues are frequently found in the environment.

The objective of this study was to determine the impact pesticides, chlorpyrifos and profenofos on oxidative stress biomarker biochemical toxicity, DNA and RNA content of male Albino mice.

Materials and Methods

Pesticides

Profenofos (Selecron, 72% E.C.) are an organophosphorous pesticide (O-(4-Bromo-2-chlorophenyl) O-ethyl S-propyl phosphorothioate; phosphorothioic acid). Relative molecular mass of the **profenofos** is 373.65g/mol and the molecular formula ($C_{11}H_{15}BrClO_3PS$) (Fig. 1).

Chlorpyrifos is a chlorinated organophosphate (OP) pesticide, acaricide and nematicide (0, 0-diethyl 0-(3, 5, 6-trichloro-2-pyridinyl) -phosphorothioate). Relative molecular mass of the **profenofos** is 350.6 g/mol and a molecular formula ($C_9H_{11}Cl_3NO_3PS$).

Profenofos and **Chlorpyrifos** were obtained from the Plants Protection Center, Ministry of Agriculture, Dokki, Giza, Egypt. (See figure 1.)

Animals

Swiss albino male mice by 10 weeks old with an average weight of 28.5±2.5 g. Mice were obtained from National Research Center, Cairo, Egypt and have been preserved in a good ventilated animal house. They were staying at a large polypropylene cage with free access to food and drinking water during the experiment and maintained under standard conditions of temperature (23°C to 25°C), a relative humidity of 65% to 86%.

Animal treatment

The animals were divided into three groups (n=6) of equal number, The control group (1) was orally and daily administered with an equivalent amount of the vehicle (distilled water) for two weeks, the second group was given drinking water with 1.5 mg/kg BW of profenofos during two weeks of oral and daily administration and the third group were orally and daily administered with Chlorpyrifos (1.5 mg /kg BW). The mice were sacrificed under diethyl ether anesthesia at fasting state at the ends of the experimental period (2 weeks).

Effect of profenofos and chlorpyrifos (pesticide) on oxidative stress biomarker, biochemical toxicity, DNA and RNA content of male albino mice

Serum samples were obtained by the centrifugation of blood of six rats of each group at 4000 rpm for 15 min at 4°C. Serum samples were divided into Eppendorf tubes. Isolated sera from each group were stored at –20°C until they were used for the analyses. For preparation of tissue homogenates of mouse liver tissue of six mice of each group, one gram of liver tissues of mouse from each group was homogenized in 5 ml distilled water at pH 7.5. The homogenate was centrifuged for 10 minutes at 3000 rpm by used a glass homogenizer. Fresh supernatant was used.

Estimation of antioxidant enzymes such as Superoxide dismutase (SOD) was measured according to Nishikimi *et al.* [13], Catalase (CAT)[14], glutathione reductase (GR)[15], lipid peroxides (LP)[16]. The levels of serum alanine aminotransferase[17] (ALT)[16], aspartate aminotransferase (AST)[17], Alkaline phosphatase (ALP)[18], acid phosphatase (ACP)[19],. Pyruvate kinase (PK)[20], phosphofructokinase (PFK)[21], Glucose phosphate isomerase (GPI)[22], Fructose -1, 6-diphosphatase (F- 1, 6-ase)[23] and Serum glucose concentrations (GL)[24]. These parameters were determined spectrophotometrically by using reagent kits purchased from BioMerieux Company, France. RNA and DNA of liver tissue were determined according to Schneider[25]. DNAase and RNAase activities were determined in liver tissues according to by Bergmeyer[26].

Statistical analysis

The Data obtained in this work were analyzed using analysis of variance (ANOVA). The significance of difference between the means was calculated using the Duncan Multiple Range Test[27].

Results

The data present in Table (3) showed that the effect of LC_{25} of Profenofos and Chlorpyrifos pesticides on some antioxidant enzymes. The result indicated that thought, there was a significant reduction in Superoxide dismutase (SOD), Catalase CAT and glutathione reductase (GR) while a significant elevation in lipid peroxides LP in treated mice compared to the normal mice. The present results showed that SOD, CAT and GR activity of mice treated with Profenofos pesticide was reduced to -41.25%, -35.63% and -33.33% 29% and LP was increased to 46.15%. The data in Table 4 demonstrates that a clear inhibition in activities of enzymes (AST, ALT and ALP) in serum of mice treated with profenofos and Chlorpyrifos pesticide as compared to the control mice. While a marked increase in the glucose level and Acid phosphatase in serum of treated mice in comparison with the control group.

The data in tables (6, 7) showed that a significant increased level of glycolytic (PK, PFK and GPI) and gluconeogenic enzyme activities (F-1, 6-D-Pase) in tissue of mice treated with profenofos and Chlorpyrifos as compared to the control. The increasing rates on the activities of PK,

PFK, GPI and F-1-6, D-Pase enzymes were 58.2%, -81.81%, -27.11% and 28.6% respectively for mice treated with profenofos.

Regarding to nucleic acids system of the liver, the contents of DNA and RNA in tissues of mice were decreased by exposing to Profenofos and Chlorpyrifos to 50, 38.46% of DNA and 42.31%, 23.1% of RNA content, respectively, relative to those of normal healthy controls. The obtained data are present in Table 3, showed that significant reductions were found in the DNAase and RNAase activity (nuclease enzymes related to the nucleic acid system) of tissue of mice treated with Profenofos and Chlorpyrifos related to healthy control. The inhibited activity in the DNAase was -39.91 and -27.78% and in RNAase was 45.83%, -19.79% for at normal control of the two nucleases activity (DNAase and RNAase). Baraldi *et al*.,[28] indicated that the oxidative stress in diabetes coexists with an inhibition in the antioxidant defense system and leads to the complications of diabetes.

Discussion

The present results found that, significant decline in SOD, CAT, and GR with significant increase in LP were observed in the tissue treated with **profenofos and Chlorpyrifos**. The reduction in the activity of free radical scavenging enzyme SOD may be due to its inactivation caused by excess ROS production. SOD neutralizes superoxide. Because it cannot cross the lipid membrane, and the production of hydrogen peroxide. Hydrogen peroxide can penetrate biological membranes. Catalase detoxifies hydrogen peroxide, which has the main role in tissue damage. Therefore, the decrease in SOD may lead to the first line of defense against enzymatic anion and hydrogen peroxide Moustafa *et al*.,[29].

In good agreement with the present results Maitlsteidt *et al*.,[30] suggested in 2004 that the nuclei and mitochondria as a key business objectives toxic MG, perhaps by increasing the generation of free radicals, lipid peroxidation and the formation of DNA adducts.

Botros *et al*.,[31] indicated that the complex mechanism of lipid peroxidation is known that requires the participation of highly reactive oxygen and other products of the reaction in a series of biochemical reaction. The present results agree with Mittelstaedt *et al*.,[30] indicated that the nuclei and mitochondria act as major targets of MG toxic action, probably by increasing the generation of free radicals, lipid peroxidation and DNA adduct formation.

Thus, thioredoxin glutathione reduced preserve high levels of reduced glutathione either through direct reduced of glutathione disulfide by thioredoxin glutathione reduced or by reducing the glutathione disulfide by thioredoxin. Therefore, thioredoxin system plays a significant role in redox balance and in the antioxidant defenses of *S. mansoni* (Algera *et al*.,[32]). Ganguly *et al*.,[33] noted that the profenofos induced dramatic changes in mitotic index when compared with nimbecidine. Kumar *et al*.,[11] indicated that Chlorpyrifos induces oxidative stress in Chroococcus turgidus NTMS12.

A powerful inference to increased activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and the content of proline and reducing the level of unsaturated fatty acids with exposed to pesticides. These changes are the defense mechanisms against the oxidative stress. Chlorpyrifos induces oxidative stress in the liver of *Oreochromis niloticus*[29].

Concerning, ALT, AST and ALP enzyme activities, gradual significant reduction were observed in serum of mice

treated with Profenofos and Chlorpyrifos for two weeks. This results agree with Bakry *et al*.[34-36] and Bakry *et al*.,[37].

The present data showed that inhibition in AST and ALT ascribes to the hepatocellular damage resulting from pesticide-toxic, where the transaminases levels showed an intimate relationship to cell necrosis and/or increased cell membrane permeability which led to the discharge of enzyme to the blood stream. The decrease in transaminase levels, providing additional support for the side effect of the Profenofos and Chlorpyrifos on the mitochondria of the hepatic cells[30]. In the present data showed that acid phosphatase shows significant increasing in serum of treated mice. Levels of acid phosphatase have been observed higher in tissues by Abdel-Rahman *et al*[38] Due to increased loss of enzyme inside cells by diffusion through the cell membrane, which show to serve as a stimulus to install more of the enzyme.

With regard to sources of energy for mice, Profenofos and Chlorpyrifos significantly increased in the sugar level of the blood of treated mice. It can be attributed to the activity of pesticides that impede consumption of oxygen of mice, which induce anaerobic respiration. Under hypoxic conditions, and animals take their energy from the anaerobic breakdown of glucose, which is available to the cells by increasing glycogenolysis[27,39].

The present data showed that significantly increased of PK, PFK and GPI (glycolytic enzymes) in liver tissue of treated mice with two pesticides compared to control group accompanied by an increase in the gluconeogenesis; F, 1-6-diphosphtase. The increase in gluconeogenic enzymes might also be responsible for producing glucose during treatment[40,41].

The present data indicated that inhibited effects of Profenofos and Chlorpyrifos on nucleases (RNAase and DNAase) activity may be due to the oxidative stress with a reduction in the antioxidant defense system[28]. Lu and Yu,[42] showed that Profenofos and Chlorpyrifos induced cytotoxicity and DNA damage by oxidative stress in mice adrenal pheochromocytoma (PC_{12}) cells. Bakry *et al*.,[43] indicated that highlights the potential ecological implications of ZnONP release in aquatic environments and may serve to encourage regulatory agencies in Egypt to more carefully monitor and regulate the industrial use and disposal of ZnONPs.

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Table 1. The effect of prolonged exposure to Profenofos and Chlorpyrifos pesticides for 2 weeks on some antioxidant enzymes in tissues of male male mice

Chlorpyrifos pesticides		Profenofos pesticide		Control	Parameters
% Change	Mean ± SD	% Change	Mean ± SD	Mean ± SD	
-37.5%	0.10±0.8	-41.25%	0.094±0.072	0.16±0.04	Superoxide dismutase (SOD)
-29.69%	59.2±0.2	-35.63%	54.2±0.12	84.2±10.2[a]	Catalase (CAT)
-42.59%	0.31+0.43	-33.33%	0.36+0.068 *	0.54± 0.32[a]	Glutathione reductase (GR)
40%	9.1+ 0.5	46.15%	9.5+ 0.61	6.5± 0.82	Lipid peroxides (LP)

* $P<0.05$ ** $P < 0.01$.
Values are means ± SD of six replicates.
Values are expressed µmol/min/mg protein while lipid peroxide is expressed in µg/g tissue

Table 2. Effect of profenofos and Chlorpyrifos pesticide on liver function enzymes in serum of male mice

		Liver function enzymes (umole/mg protein/min.)						Glucose (GL) mg/g tissue		
Acid phosphatase (ACP)		ALP		ALT		AST				
% Change		% Change		% Change		% Change		% Change		
	7.2 ±1.4		4.2 ±0.2		9.5 ±0.4		16.33 ±1.2		28.4 ±0.8	Control
-26.38%	9.1 ±0.1	-23.81%	3.2 ±0.23	38.95%	5.8±0.12	18.55%	13.3±0.2	49.7%	45.2±0.44	Profenofos
-12.5%	8.1 ±0.6	-9.52%	3.8 ±0.42	32.63%	6.4 ±0.16	22.84%	12.6 ±1.2	49.6%	42.5±0.38	Chlorpyrifos

Data represent mean values of five replicates. Within columns for dose, time and (dose x time), mean values followed by different letters are statistically significantly different based on LSD at P = 0.05.

Table 3. Effect of profenofos and Chlorpyrifos on some glycolytic and gluconeogenic enzymes in male mice liver

Gluconeogenic enzymes		Glycolytic enzmes (umole/mg protein/min.)						
Fructose-1, 6 diphos-phatase (umole/mg protein/min.)		GPI		PFK		PK		
% change		% change		% change		% change		
	14.5±1.5		88.43 ±1.5		8.3 ±1.4		5.12 ±0.51	Control
15.86%	16.8 ±1.4	-27.11%	112.4 ±1.5	-81.81%	12.6±1.6	-58.2%	8.1 ±1.7	Profenofos
28.6%	18.65 ±1.61	-17.15%	103.6 ±3.2	-26.51%	10.5±1.5	-28.91%	6.6 ±1.3	Chlorpyrifos

Data represent mean values of five replicates. Within columns for dose, time and (dose x time), mean values followed by different letters are statistically significantly different based on LSD at P = 0.05.

Table 4. Effect of profenofos and Chlorpyrifos on on DNA and RNA contents in male mice

	RNAase IU/g		DNAase IU/g		RNA mg/g	%	DNA mg/g	Treatments
	48 ± 0.64		64.24 ± 1.2		0.26 ± 0.08		0.52 ± 0.034	Normal control
-45.83%	26 ± 0.64	-39.91	38.6 ± 0.6	42.31	0.15 ± 0.003	50	0.26 ± 0.14	Profenofos
-19.79%	38.5 ± 1.6	-27.78	46.4 ± 1.8	23.1%	0.20 ± 0.18	-38.46%	0.32 ± 0.27	Chlorpyrifos

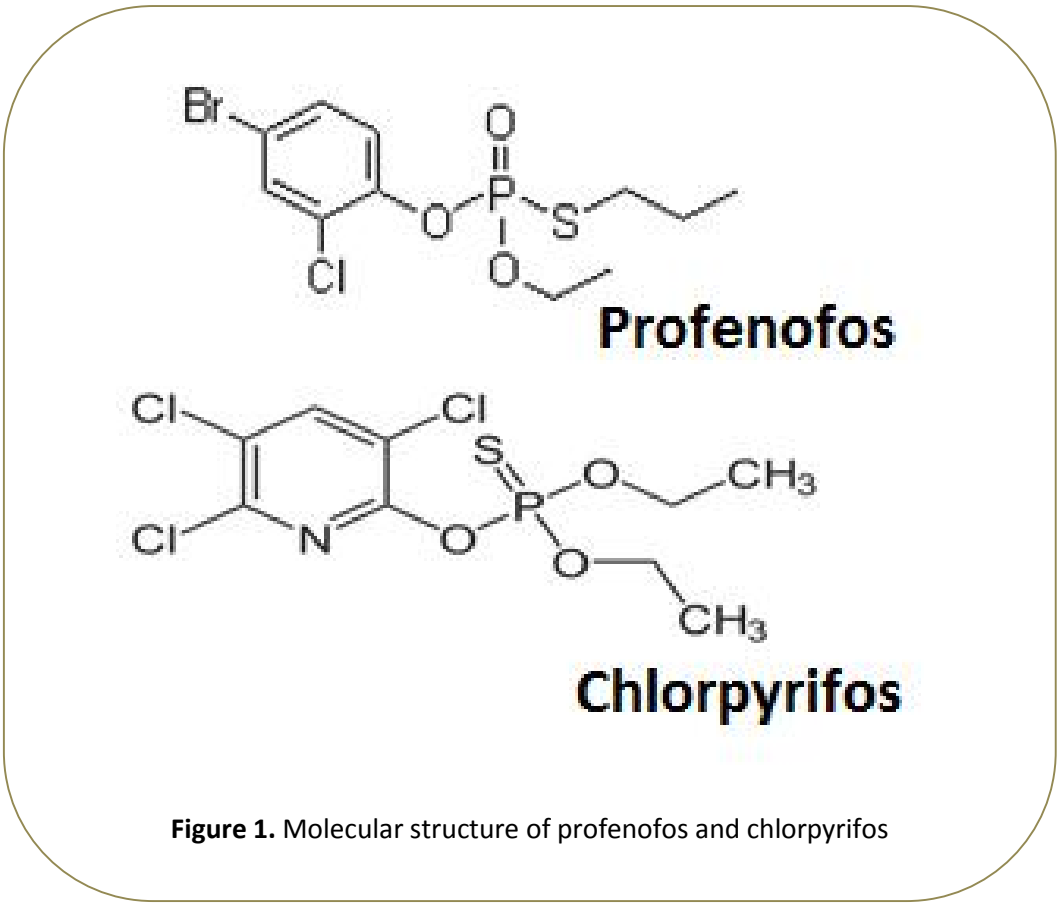

Figure 1. Molecular structure of profenofos and chlorpyrifos