Fate of <sup>14</sup>C-ethyl Profenofos in Soybean Seeds and Oils, Residue Removal, Bioavailability, Toxicity and Protective Action of Cinnamon Extract towards Experimental Animals

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HE TOPICAL application of <sup>14</sup>C- profenofos on soybean plant led to the appearance of 10 ppm <sup>14</sup>C-residues in the dry seeds at harvest time. Commercial processing procedures led to a gradual decrease in the total amount of <sup>14</sup>C-residues in oils. The complete refined oil from treated seeds lost about 80% of the total <sup>14</sup>C-residues. The major part of <sup>14</sup>C-residues after feeding rats with the extracted soybean seeds for 72 hr was eliminated via expired air (45%) while radioactivity in urine and feces accounted for 18% and 12% of the taken <sup>14</sup>C- residues, respectively. The results revealed that profenofos residues induced abnormal hepatic and renal function which was remarkably attenuated with co-administration of water extract of cinnamon powder thereby suppressed the deviation in the liver and kidney function markers. From the present investigation it can be concluded that the used plant extract exerted prophylactic beneficial action against profenofos induced hepatic and renal damage via its antioxdating potential effects.

**Keywords:** <sup>14</sup>C-Profenofos residues, Commercial processing, Bioavailability, Toxicity, Cinnamon and Protective effect.

Organophosphate (OP) compounds are the most toxic chemicals that are used in widespread applications. These compounds have been widely used in agriculture for crop protection and pest control <sup>(1)</sup> and caused severe environmental pollution and potential health hazards including severe acute and chronic cases of human and animal poisonings <sup>(2, 3)</sup>. Toxicities of OP insecticides cause adverse effects on many organs <sup>(4)</sup>. Systems that could be affected by OPs are the immune system<sup>(5)</sup>, liver <sup>(6)</sup>, muscles <sup>(7)</sup> urinary system <sup>(8)</sup>, reproductive system <sup>(9)</sup>, pancreas <sup>(10)</sup> and hematological system <sup>(11)</sup>.

Profenofos, *O*-[4-bromo-2-chlorophenyl] *O*-ethyl *S*-propyl phosphorothioate (Selecron) is a widely organophosphorus insecticide used in Egypt for the control of various caterpillars, white fly and mites on cotton and vegetable crops <sup>(12)</sup>. Profenofos is reported to be highly toxic to human, animals and aquatic organisms <sup>(13-15)</sup>. Its main physiological effect is the inhibition of cholinesterase (ChE) activity <sup>(16)</sup>.

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Soybean oil is a concentrated, hydrophobic liquid containing volatile aromatic compounds extracted from soybean (Glycine max). Soybean oil is popularly used in food processing and cooking. Soybean oil accounts for over 75% of the total vegetable oil in human foods (17).

Cinnamon (*C. zeylanicum*, Family *Lauraceae*) is a popular flavoring ingredient, widely used in food products. It has exhibited beneficial properties to health, such as antimicrobial activity, for controlling glucose intolerance and diabetes, inhibiting the proliferation of various cancer cell lines and for treating the common cold<sup>(18,19)</sup>. In Eastern and Western folk medicine it is used for treating abdominal and chest pains, chronic diarrhea, hypertension, kidney disorders and rheumatism. Intake of 3g or 6g of cinnamon bark reduced serum glucose in people with type 2 diabetes<sup>(20)</sup>. Cinnamon extracts have also demonstrated hepatoprotective and antioxidant effects in CCL4-intoxicated rats<sup>(21)</sup>.

The objectives of the present study are (1) determination and identification of profenofos residues in soybean seeds and oils, (2) deducing the effect ofrefining processes on the level and nature of <sup>14</sup>C-labelled profenofos residues in crude soybean oil, (3) investigation the bioavailability of its bound residues in rats and (4) studying the effect of subchronic exposure to profenofos residues as well as the protective action of cinnamon on rats.

#### **Material and Methods**

Chemicals

<sup>14</sup>C-ethoxy profenofos (I) has been prepared according to Hegazi *et al.* <sup>(22)</sup> in one vesseled reaction by condensation of equimolar amounts of 4-bromo-2-chlorophenol with *S*-propyl phosphorodichloridothioate followed by dropwise addition of <sup>14</sup>C-ethanol as follows:

Synthesis of 4-bromo-2-chlorophenol

A mixture of bromine (0.1 mole,  $5.1 \,\mathrm{ml}$ ) was added dropwise to 2-chlorophenol (0.1 mole,  $10.4 \,\mathrm{ml}$ ) in presence of glacial acetic acid (20 ml). Thereaction mixture was stirred for four hours until complete removal of HBr. Pour into ice and water, filter, recrystalization from water, gave high yield (88 %) of the title compound, mp. 47-49 °C (Scheme 1).

$$CI$$
 $OH$ 
 $Br_2$ 
 $acetic\ acid$ 
 $Br$ 
 $OH$ 

2-chlorophenol

4-bromo-2-chlorophenol

Scheme 1. Synthesis of 4-bromo-2-chlorophenol.

Synthesis of S-propyl phosphorodichloridothioate

S- propyl phosphorodichloridothioate was synthesized by reaction of propyl mercaptane (0.2 mole) in a mixture of benzene and toluene (1:5 v/v) with (0.22 mole) sulfuryl chloride for 1 hr at -3°C, followed by addition of glacial acetic acid and (0.2 mole) phosphorus trichloride in dry benzene. The mixture was stirred for 2 hr, the reaction mixture left overnight followed by vacuum distillation giving a brown viscous oil of S-propyl phosphorodichloridothioate (b.p.105-110°C at 15 mmHg) with 80 % yield.

# Synthesis of <sup>14</sup>C-ethoxy profenofos (I)

A mixture of 4- bromo-2- chlorophenol (0.0048 mole, 1g) and triethylamine (0.0096, 1.4ml) in dry benzene was added dropwise to a cooled (10°C) solution of *S*-propyl phosphorodichloridothioate (0.0048 mole, 1g) in dry benzene during 20 min. Stirring was continued for 4 hr, followed by dropwise addition of <sup>14</sup>C- ethyl alcohol (0.0048 mole, 3ml, 37 MBq) in dry benzene. The reaction mixture was stirred at 25°C for 18 hr and filter. The filtrate was washed twice with cold distilled water and dried over anhydrous sodium sulfate. The crude oil (sp.act. 12.2 MBq/g, 78 % yields) was purified on silica gel column using hexane: ethyl acetate (4:1) for elution. The radiochemical purity was greater than 98 % (Scheme 2).

Br 
$$\longrightarrow$$
 OH + CI  $\longrightarrow$  CI  $\longrightarrow$  CI  $\longrightarrow$  CI  $\longrightarrow$  O  $\longrightarrow$  CI  $\longrightarrow$  CI

Scheme 2. Synthesis of <sup>14</sup>C-ethyl profenofos.

A labeled preparation of specific activity 11.8 kBq/mg was obtained by dilution of <sup>14</sup>C-labeled insecticide with non-labeled profenofos (prepared in our laboratory). Some degradation products, which are required for identification purposes have been synthesized according to the procedures reported by Hegazi *et al.* <sup>(22)</sup>. These were *O*-(2-chlorophenyl) *O*-ethyl *S*-propyl phosphorothioate (II), *O*-ethyl *S*-propyl phosphorothioate (III), *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphate (IV) and *O*-(4-bromo-2-chlorophenyl) *S*-propyl phosphorothioate (V).

#### Cultivation

Soybean seeds (var. Crawford) were cultivated in an isolated and controlled area. Plants were irrigated and fertilized as in practice. The aqueous suspension of <sup>14</sup>C-profenofos (4 mg/plant each time) was topically applied manually with a micropipette on healthy leaves of plants twice (21 days apart) just before the flowering stage. Soybean pods were collected at 30 days after the second spray of labeled profenofos (harvest time). The <sup>14</sup>C-residues in dry seeds were determined by digestion followed by liquid scintillation counting.

## Toxicological studies

In order to study the toxicological potential of profenofos residues in soybean seeds and the protective effect of cinnamon, a subchronic feeding study on rat for 30 days was carried out. White male albino rats weighting about 100 g were obtained from the animal house in National Research Centre, Dokki, Cairo. The rats were housed in stainless steel cages with a maximum of four rats per cage provided with a free supply of feed and water. These were randomly divided into four groups as follow:

- Group 1: control rats fed on normal diet free from pesticide.
- Group 2: control rats fed on normal diet free from pesticide and 1% w/w cinnamon extract.
- Group 3: rats fed on soybean seeds containing 10 ppm profenofos residues.
- Group 4: rats fed on soybean seeds containing 10 ppm profenofos residues and 1% w/w cinnamon extract.

## Preparation of cinnamon extract

Fine dried powder of cinnamon bark was obtained from a commercial market. Ten grams of cinnamon powder were homogenized with 200 ml of distilled water. Cinnamon homogenate was carefully centrifuged and the supernatant was incorporated in 1 kg of control and treated soybean seeds and mixed manually for at least 30 min to ensure complete distribution.

#### Oil extraction

Dry soybean seeds were crushed and extracted with n-hexane for 12 hr using a Soxhlet apparatus. After evaporation of hexane under reduced pressure, radioactivity in the soybean oil was measured. The residue remaining after extraction was further extracted with 95% methanol. Aliquots of the hexane extract (oil) and the methanol extract were used for determination of  $^{14}\mathrm{C}$ -residues. The remaining cake was air dried and digested by adding 1 ml Solusol (tissue and gel solubilizer) and digest samples at 40-50°C until tissue dissolves, decolorize with 30%  $\mathrm{H_2O_2}$  (1ml) and add 70  $\mu\mathrm{L}$  glacial acetic acid to eliminate chemiluminescence  $^{(23)}$ . The radioactive residue was determined by using liquid scintillation counter.

#### Removal of pesticide residues from oils

The crude oil (20g) was stirred vigorously with 2N sodium hydroxide solution (2ml) for about 30 min at 27°C. The mixture was then centrifuged to

remove the soap and excess alkali, washed several times with warm water until pH 7.0 and centrifuged to obtain the clear oil.

The alkali refined oil was treated with 0.5% (by weight) of a factory grade Fuller's earth (Tonsil), the mixture stirred vigorously at 80-100°C for 20 min and then centrifuged. The bleached oil was filtered.

The clear dry oil was chilled at 5°C for three days and the separated high saturated glycerides were removed by centrifugation.

Superheated steam was passed into the heated oil at about 200°C under reduced pressure, for three hours, to remove steam-distillable substances including odors. Aliquots of oil, after each refining process, were analyzed for their radioactive residues.

Isolation and characterization of <sup>14</sup>C-residues

Analysis of radioactive compounds was achieved by thin layer chromatography (TLC). Samples of crude oil after one month of the last treatment and after each refining process were partitioned between acetonitrile and hexane three times to remove the oil. The radioactive residues were distributed between the two layers. Analysis of crude and refined oil extracts were achieved by thin layer chromatography (TLC) on silica gel plates [Mercksilica gel  $60 \ F_{254}$ ]. The solvent systems used were.

System 1: n-butanol: acetic acid: water	35: 3: 10	(v/v)
System 2: ethyl acetate: ethanol: acetic acid	9: 9:1	(v/v)
System 3: acetonitrile: water: ammonia	40: 9: 1	(v/v)

Generally, the free metabolites were detected by TLC. The conjugated metabolites were liberated by heating the mixture with 2N HCl (25ml) for 2 hr at 100°C. After cooling, the mixture was extracted with chloroform for three times, the combined chloroform was dried over anhydrous sodium sulfate, filtered off, evaporated under vacuum and identified by TLC analysis using the solvent system, heptane: chloroform: methanol (9: 4: 1).

Authentic samples were run alongside as references and spots were made visible by exposing to UV- source and by spraying the plates with a freshly prepared Hans-Isherwood reagent or by subjecting to  $I_2$  vapour, after preliminary spray with  $PdCl_2$  solution  $^{(25,26)}$ . To detect the phenolic compounds, the plate was sprayed with a freshly prepared solution of ferric chloride potassium ferricyanide, where blue spots against yellow background appeared  $^{(27)}$ .

The radioactivity in oil (acetonitrile extract or methanol extracts) was measured directly by liquid scintillation counting (LSC) (Packard Model TRI-CARB 2300 TR) in vials using a dioxane-based scintillation cocktail which composed of dioxane (1L), naphthalene (100 g),[PPO; 2,5-diphenyloxazole](10g) and POPOP; 1,4-di[2-(5-phenyloxazolyl)]-benzene (0.25g). Radioactivity in

seeds or cakes (100mg) was determined by digestion using  $H_2O_2$  (1ml) and Solusol followed by liquid scintillation counting. Silica gel plates were separately scrapped (1cm zones) and silica gel was eluted with methanol followed by LSC. The counts were corrected for background and quenching effect by channel ratio method.

#### Bioavailability of bound residues in rats

White male albino rats weighting about  $150\pm10$  g were purchased from animal house colony, N R C, Dokki, Giza Egypt. The animals were individually housed in glass metabolism cages that allowed separate collection of feces, urine and expired air. The rats were conditioned for two days for acclimation under the laboratory conditions ( $29\pm3$  °C). The animals were kept without food for 24 hr and then fed the diet containing bound <sup>14</sup>C-profenofos residues for three days. To make the feed palatable, the extracted seeds were mixed thoroughly with an equal amount of white cheese and the paste was left to dry. The carbon dioxide was trapped in 10% NaOH solution. Urine, feces and <sup>14</sup>CO<sub>2</sub> were collected separately for three days, and assayed for radioactivity. At the end of the experimental period rats were anaesthetized with ether and samples from liver, kidney, fat, blood, were collected and kept frozen till analysis of <sup>14</sup>C-residues by digestion and followed by LSC-counting.

#### Toxicological studies

At the end of the experimental period (30 days) rats were anaesthetized with ether. Blood samples were collected from orbital venous plexus in heparinized and non-heparinized tubes. The blood in the heparinized tubes was immediately used for the assay of cholinesterase activity. The blood in non-heparinized tubes was centrifuged at 3000 rpm for 20 min for other biochemical parameters. Cholinesterase activity was determined according to Ellman Method <sup>(28)</sup> as modified by Gorun *et al.* <sup>(29)</sup>. The liver parameters [Alanine aminotrasferase (ALT), Aspartate aminotrasferase (AST), alkaline phosphates (ALP), total protein and albumin], kidney parameters (urea and creatinine), lipid profile (cholesterol, triglycerides) and antioxidant parameters [Catalase (CAT) and Glutathione-S- Transfrase (GST)] were determined by using local kits (from Biodiagonostic Company in Egypt).

### Statistical analysis

The obtained data from serum biochemical and enzymes analysis were statistically evaluated for the mean and standard error of the mean of each group. The significance of the changes between the tests and the control group was evaluated by the "t" test according to Sendecor and Cochran <sup>(30)</sup>.

## **Results and Discussion**

The topical application of <sup>14</sup>C- profenofos on soybean plant led to the appearance of <sup>14</sup>C-residues in the dry seeds and amounted to 10 ppm at harvest time (30 days). The insecticide was absorbed and translocated very slowly from *Egypt. J. Chem.* **54**, No. 2 (2011)

<sup>&</sup>lt;sup>14</sup>C-residues in seeds, oil and cake

the treated leaves to the seeds of investigated plant, and decreased due to the enzyme metabolic activity <sup>(31)</sup>. The <sup>14</sup>C-residues in dry soybean seeds obtained from <sup>14</sup>C- profenofos treated plants amounted to 0.02 % of the originally applied dose. The foliar treatment of soybean plants with <sup>14</sup>C-pirimiphos-methyl lead to appearance of <sup>14</sup>C-residues in the mature seeds. These amounted to 0.37% of the applied dose <sup>(32)</sup>. The activity in extractable <sup>14</sup>C-residues in crude oils was 6.48 ppm and 0.57 ppm for both hexane and methanol extracts, respectively 30 days of the second application. The non-extractable (bound) residues were 2.43 ppm and the percent of total recovery was 94.8 % as shown in Table 1. The persistent insecticides are beneficial for controlling pests for extended period however; their residues in consumable parts of the crops may be harmful to the consumers in case of being higher than the Maximum Residue Limit (MRL) values <sup>(33)</sup>. Research on sunflower seeds and oil treated with endosulfan and lindane were exceeded the MRLs value in sunflower seeds at harvest <sup>(34)</sup>.

TABLE 1. Distribution of <sup>14</sup>C-profenofos residues in soybean seeds.

Fraction	<sup>14</sup> C-residues (ppm) <sup>a</sup>	% b
Soybean seeds	$10.0 \pm 0.85$	100
Oil	$6.48 \pm 0.35$	64.8
methanol	$0.57 \pm 0.11$	5.7
cake	$2.43 \pm 0.28$	24.3
Total recovery	9.48	94.8

a: Results are expressed as mean  $\pm SD$  for three determinations of profenofos residue level for each sample.

## Effect of refining processes

Commercial processing procedures led to a gradual decrease in the total amount of <sup>14</sup>C-residues in oils as shown in Table 2. The complete refined oil from treated seeds lost about 80% of the total <sup>14</sup>C-residues in crude oil. This decrease could be attributed to alkali hydrolysis, effect of adsorption, effect of heat and/or evolved <sup>14</sup>CO<sub>2</sub> gas. Tayaputch et al. <sup>(35)</sup> found that during the processing of crude soybean oil, alkali treatment removed 50%, while deodorization reduced the residues of <sup>14</sup>C- prothiofos by further 25%. Also, the present results seem to be in agreement with those reported by Zayed et al. (32, 36) who showed that the amounts of both <sup>14</sup>C- carbofuran and <sup>14</sup>C-pirimiphos-methyl residues in soybean oil decreased to 16% and 25% through the refining processes, respectively. Working on cotton oil grown with <sup>14</sup>C-aldicarb, 63% of the residues in cured oil were also found to be lost during the refining processes (37). The effect of processing methods used for oil refining on <sup>14</sup>C-Zineb residues was studied. Obvious reduction was detected by neutralization (31.7%) and was increased by further bleaching (34.1%), chilling (41.46%) and deodorization (63.6%) methods (38).

b: Total  $^{14}$ C-in seeds = 100%.

TABLE 2. Effect of refining process on <sup>14</sup>C-profenofos residues in soybean oil.

Sample	<sup>14</sup> C- residues (ppm) <sup>a</sup>	% Reduction <sup>b</sup>
Crude oil	$6.48 \pm 0.35$	0.0
Neutralized oil	$3.78 \pm 0.64$	41.6
Bleached oil	$2.58 \pm 0.71$	60.2
Chilled oil	$1.98 \pm 0.35$	69.4
Deodorized oil	$1.28 \pm 0.49$	80.2

a: Results are expressed as mean  $\pm SD$  for three determinations of prothiofos residue level for each sample.

Identification and characterization of radioactive degradation products in oil

the degradation products of  $^{14}\text{C}$ - profenofos in crude oil (hexane extract) and their amounts (ppm) at the end of 30 days of the second treatment of soybean plants were illustrated in Table 3. In addition to the parent compound (I), O-(2-chlorophenyl) O-ethyl S-propyl phosphorothioate (II), O-ethyl S-propyl phosphorothioate (III) and O-ethyl phosphoric acid (VI) were identified as the main degradation products, besides to one unknown compound. The unknown compound which proved to be hydrophilic product, tlc analysis of it had  $R_f$  value of (0.85), (0.45) and (0.65) in solvent systems n-hexane: ethyl acetate 99.5: 0.5, n-heptane ethyl acetate 99:1 and n-heptane, respectively.

Chromatographic analysis of methanol extract revealed the presence of *O*-ethyl *S*-propyl phosphorothioate (III), *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphate (IV) and *O*-ethyl phosphoric acid (VI) as free metabolites in addition to conjugated metabolites. These were liberated by acid hydrolysis and identified as 4-bromo-2-chlorophenole and 2-chlorophenole; the latter compounds were detected by color.

TABLE 3. The amount and R <sub>f</sub> values of <sup>14</sup>C- profenofos and its active degradation products in extracts of soybean seeds and oil after 30 days of treatment.

	R <sub>f</sub> in systems			Acetonitrile	Methanol
Substances	1	2	3	Extract	Extract
				(ppm)	(ppm)
Profenofos (I)	0.92	0.85	0.91	0.99	0.00
O-(2-chlorophenyl)O-ethyl					
S-propyl phosphorothioate (II)	0.83	0.90	0.89	0.96	0.00
O-ethyl S-propyl					
phosphorothioate (III)	0.66	0.60	0.53	3.17	0.07
O-(4-bromo-2-chlorophenyl)					
O-ethyl phosphate (IV)	0.75	0.77	0.56	0.00	0.08
O-ethyl phosphoric acid (VI)	0.44	0.23	0.08	1.35	0.25
Unknown	0.15	0.00	0.00	0.00	0.17

System 1: n-butanol: acetic acid: water 35: 3: 10 (v/v)
System 2: ethyl acetate: ethanol: acetic acid 9: 9: 1 (v/v)
System 3: acetonitrile: water: ammonia 40: 9: 1 (v/v)

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b: % Reduction = [(crude oil-each step) /crude oil] x 100

The suggested pathway for the degradation of <sup>14</sup>C-profenofos in soybean plant is shown in Scheme 3. *O*-(2-chlorophenyl) *O*-ethyl *S*-propyl phosphorothioate (II) is formed by reductive debromination of the parent compound. Cleavage of the phenolic ester bond leads to the formation of *O*-ethyl *S*-propyl phosphorothioate (III) and free 4-bromo-2-chlorophenole and 2-chlorophenol which are further conjugated with sugar in the plant. Depropylation and scission of sulfur leads to the formation of *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphate (IV) and *O*-ethyl phosphoric acid (VI). Katagi and Mikami <sup>(39)</sup> noted that the metabolism of organophosphorus pesticides in plants have revealed cleavage of the P-O-aryl linkage and *O*-dealkylation to be among the most predominant metabolic pathways. Enzymatic and acid hydrolysis release an aglycon and direct spectroscopic analyses of metabolites implied that the insecticide primarily underwent cleavage of the P-O-aryl linkage or hydroxylation of the aryl methyl group similarly to other organophosphorus pesticides in plants.

Scheme 3. Proposed pathways for degradation of <sup>14</sup>C- profenofos in soybean plant.

The degradation products of <sup>14</sup>C-profenofos in crude and refined oil (hexane extract) and their amounts (ppm) in the oil following the individual processing procedures at the end of 30 days of the second treatment of soybean plants were illustrated in Table 4. In addition to the parent compound (I), *O*-(2-chlorophenyl) *O*-ethyl *S*-propyl phosphorothioate (II), *O*-ethyl S-propyl phosphorodithioate (III), *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphate (IV) and *O*-ethyl phosphoric acid (VI) were identified as the main degradation products, besides to one unknown compound. Their amounts decreased during the refining steps.

TABLE 4. <sup>14</sup>C-profenofos and its degradation products in soybean oil after subjecting to refining process .

	<u>R<sub>f</sub> in systems</u> <u>Metabolites residues ( ppm )</u>			ppm )				
Substances	1	2	3	Crude oil	A	В	C	D
Profenofos (I)	0.92	0.85	0.91	0.99	0.00	0.00	0.00	0.00
O-(2-chlorophenyl) O- ethyl S-propyl phosphorothioate (II)	0.83	0.90	0.89	0.96	0.75	0.54	0.52	0.38
O-ethyl S-propyl phosphorothioate (III)	0.66	0.60	0.53	3.17	0.85	0.60	0.53	0.45
O-(4-bromo-2- chlorophenyl)O-ethyl phosphate (IV)	0.75	0.77	0.56	0.00	0.47	0.30	0.00	0.00
O-ethyl phosphoric acid (VI)	0.44	0.23	0.08	1.35	0.71	0.48	0.40	0.00
Unknown	0.15	0.00	0.00	0.00	0.94	0.66	0.52	0.38

A : Neutralization B: Bleaching C: Chilling D: Deodorization

System 1: n-butanol: acetic acid: water 35: 3: 10 (v/v)
System 2: ethyl acetate: ethanol: acetic acid 9: 9:1 (v/v)
System 3: acetonitrile: water: ammonia 40: 9: 1 (v/v)

#### Bioavailability in rats

Elimination and distribution of <sup>14</sup>C-residues Following feeding rats with the extracted soybean seeds for 72 hr are shown in Table 5. It was observed that the major part of residues was eliminated via expired air (45%) while residues in urine and feces accounted for 18% and 12% of the applied dose, respectively. Appreciable amount of <sup>14</sup>C- residue (15%) was also detected in liver, kidney, blood and fat of treated rats. The bound profenofos residues in diet appear to have no effect on the body weight gain of the treated rats. Analysis of urine showed the presence of *O*-ethyl *S*-propyl phosphorothioate (III), *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphate (IV) and *O*-ethyl phosphoric acid (VI) as free metabolites in addition to conjugated metabolites. These were liberated by acid hydrolysis and identified as 4-bromo-2-chlorophenole and 2-chlorophenole.

Bound <sup>14</sup>C-profenofos residues in soybean seeds proved to be highly bioavailable to rats. Similar results were reported from studies on the bioavailability of soybean bound residues of pirimifos methyl <sup>(40)</sup>,

chloropyrofos<sup>(41)</sup>, dichlorovos <sup>(42)</sup> and fenitrothion <sup>(43)</sup>. Also, the data obtained are in line with many other studies which indicate a moderate to high bioavailability of grains bound <sup>14</sup>C-pesticide residues in experimental animals <sup>(44-46)</sup>.

TABLE 5. Excretion and distribution of <sup>14</sup>C-profenofos residues bound to soybean seeds which had fed to rats for 72hr.

Sample	Insecticide equivalent* (µg)	Percentage of administration dose
Carbon dioxide	33.75±0.8**	45
Urine	13.50±1.1	18
Faces	9.00±2.0	12
Blood	3.00±0.14	4
Liver	4.50±0.15	6
Fat	2.25±0.16	3
Kidney	1.50±0.12	2
Total Removal	67.5	90

<sup>\*</sup> Administration dose = 100% (75µg equivalent per rat)

#### Toxicological studies

Effect on cholinesterase activity

Acetyl Cholinesterase (AChE) activity in serum was significantly (78.4%, P< 0.02) inhibited in profenofos-treated rats (group 3) as compared to control (Table 6). Cinnamon - treated rats administered with profenofos (group 4) showed high removal rate compared to profenofos-treated rats (group 3). Cholinesterase is an enzyme necessary for proper nerve impulse transmission. If the activity of this enzyme is reduced below a critical level, nerve impulses to the muscles can no longer be controlled, resulting in serious consequences and even death. However, the serum cholinesterase inhibition has been recommended due to acute toxicity of organophosphates results from the irreversible phosphorylation of the hydroxyl group located in the active site of the molecule (47). These results are in accordance with those findings obtained by several authors (48-52) who concluded that ChE activity was significantly decreased after exposure of rats to organophosphorus pesticides.

TABLE 6. Effect of water extract of cinnamon on plasma-cholinesterase activity in normal and profenofos treated rats.

	ChE activity		
Groups	(μ mole/ml)	Percentage of control	
	Mean <sup>a</sup> ± SD	(%)	
Control	$1.62 \pm 0.043$	100	
Control & Cinnamon	$1.67 \pm 0.047$	103	
Profenofos	1.27 ± 0.047**	78.4	
Profenofos & Cinnamon	$1.58 \pm 0.020$	97.5	

a: Results are expressed as mean  $\pm$  SD for four samples.

<sup>\*\*</sup> Results are expressed as mean ± SD for three determinations of profenofos residue level for rats.

<sup>\*\*:</sup> Significance at P< 0.02

#### Effect on liver functions

Table 7 shows the activities of serum ALT, AST and ALP as well as the levels of serum total protein and albumin as markers evaluate liver function in tested animals in different experimental groups. From the table it can be observed that profenofos intoxication to rats (group 3) induced liver tissue damage indicated by elevated levels of ALT, AST and ALP with concomitant decrease in total protein and albumin levels in relation to normal group (group 1) (P<0.01 for all tested parameters). These results are supported by previous biochemical studies that showed alteration of such biomarkers in experimental animals and humans exposed to organophosphorus insecticides, profenofos<sup>(51,53)</sup>, fenitrothion<sup>(54,55)</sup>, chlorpyrifos (56) and diazinon (57). Co-administration of water extract of cinnamon to profenofos treated rats (group 4) daily for 30 days along with profenofos residues greatly prevented the deviation in the liver function indices in relation to profenofos residues treated rats (group 3). The reduction of AST and ALT activities by the cinnamon extract is an indication of repair of hepatic tissue damage induced by profenofos residues; our results are in agreement with those obtained by administration of water extract of cinnamon to intoxicated animals with CCl4 induced suppression of increased ALT and AST activities in rats and frogs (21,58). Thus, administration aqueous extracts of cinnamon revealed hepatoprotective activity against the toxic effect of profenofos.

TABLE 7. Effect of water extract of cinnamon on liver function in normal and profenofos treated rats.

Group	ALT (U/L)	AST (U/L)	Alk.phosphatase ( U/L)	T.protein ( g/dL )	Albumin ( g/dL )
	Mean ± SD <sup>a</sup>	Mean ± SD <sup>a</sup>	Mean ± SD <sup>a</sup>	Mean ± SD <sup>a</sup>	Mean ± SD <sup>a</sup>
Control	$30.3 \pm 2.2$	79.5 ±3.1	208 ±8.79	$6.95 \pm .31$	$2.95 \pm 0.08$
Control & Cinnamon	$29.5 \pm 1.3$	$81.0 \pm 2.16$	$208 \pm 6.73$	$6.93 \pm 0.17$	$2.95 \pm 0.078$
Profenofos	54.3±5.70***	104.5±5.97***	251.5 ± 9.57***	5.98±0.18***	2.54±0.075***
Profenofos & Cinnamon	$32.8 \pm 2.50$	83.75 ±2.21	$212.5 \pm 8.06$	$6.83 \pm 0.33$	2.88 ±0.061

a: Results are expressed as mean  $\pm$  SD for four samples.

### Effect on kidney functions

Daily exposure of rats to profenofos residues was also shown by this study to cause marked elevated levels (P< 0.01) of serum kidney function indices, urea and creatinine, in relation to control group (Table 8). Kidney is one of the targets organs of experimental animals attacked by OP compounds<sup>(59,60)</sup>. It was suggested that uremia was due to increase catabolism of body proteins, decreased renal blood flow as a result of general circulatory distress or renal damage from the pesticide. Our results were coincided with Manal and Yousef <sup>(51)</sup> and Rahman and Siddiqui <sup>(61)</sup> .Treatment with cinnamon significantly prevented the elevation of urea and creatinine levels. This is in agreement with Mohamed *et al.* <sup>(54)</sup> who found that blood urea and serum creatinine returned to normal activities with coadministration of butanolic extract of *Myoporum laetum* leaves to rats treated

<sup>\*\*\*:</sup> Significance at P< 0.01

with repeated doses of profenofos. Also, Elhalwagy et al. (55) found that green tea had prophylactic effect against kidney injury induced by fenitrothion insecticide.

TABLE 8. Effect of water extract of cinnamon on kidney functions in normal and profenofos treated rats.

Group	Urea (mg %)	Creatinine (mg %)
	Means <sup>a</sup> ± SD	Means <sup>a</sup> ± SD
Control	$0.84 \pm 0.034$	$56.5 \pm 3.41$
Control & Cinnamon	$0.85 \pm 0.044$	$53.8 \pm 2.98$
Profenofos	1.10 ±0.059***	75 ± 4.39***
Profenofos & Cinnamon	$0.87 \pm 0.034$	$61.5 \pm 3.41$

Results are expressed as mean  $\pm$  SD for four sample.

### Effect on lipid profile

Profenofos residues significantly increased the levels of serum cholesterol and triglyceride in treated animals (Table 9). These results were in agreement with Mogda et al. (53) and Yousef et al. (62). The elevated of serum cholesterol and triglycerides were significantly reduced in the animal groups treated with cinnamon extract (Table 9). These results were in agreement with Moselhy and Ali (21) in the study of protective effect of cinnamon on CCl<sub>4</sub> intoxicated rats.

TABLE 9. Effect of water extract of cinnamon on lipid profile in normal and profenofos treated rats

Group	Cholesterol (mg %)	Triglycerides (mg %)
	Means <sup>a</sup> ± SD	Means <sup>a</sup> ± SD
Control	$105.3 \pm 5.6$	$94.0 \pm 5.94$
Control & Cinnamon	$101.0 \pm 6.2$	$87.0 \pm 2.58$
Profenofos	124.0 ± 5.16**	119.0 ± 5.29***
Profenofos & Cinnamon	$107.0 \pm 3.82$	$97.0 \pm 6.27$

a: Results are expressed as mean  $\pm$  SD for four samples.

Effect on the activities of different antioxidant enzymes ( Catalase, CAT and *Glutathion –S- Transferase, GST)* 

The activities of serum antioxidants CAT and GST decreased significantly (p < 0.02 and p < 0.01, respectively) in profenofos - treated rats, while treatment with cinnamon significantly prevented this decrease in levels of the two parameters (Table 10) when compared with the profenofos-treated rats. Literature report suggests that free radical mediated oxidative stress is responsible for the toxicity of pesticides<sup>(63,3)</sup>. Reduction in the activities of CAT suggests their depletion in neutralizing the profenofos-induced reactive oxygen species (ROS). CAT is the first line of defense against the toxic intermediates of oxygen Egypt. J. Chem. 54, No. 2 (2011)

<sup>\*\*\*:</sup> Significance at P< 0.01

<sup>\*\*:</sup> Significance at P< 0.02

<sup>\*\*\*:</sup> Significance at P< 0.01

metabolism. GST is involved in the detoxification pathway for organophosphorus compounds that detoxifies xenobiotics, catalyzes the binding of wide variety of electrophiles including insecticides and environmental polluted to glutathione (GSH) to form less toxic conjugated that are readily eliminated by excretion  $^{(64)}$ . Studies have shown that antioxidants and plant extracts can play a protective role in inhibiting pesticide-induced toxicity  $^{(65, 66)}$ . Our results were in agreement with Moselhy *et al.*  $^{(21, 58)}$  and Mohamed *et al.*  $^{(54)}$  in their study of protective effect of *myoporum laetum* against oxidative stress induced by profenofos in rats.

TABLE 10. Effect of water extract of cinnamon on antioxidant enzymes catalase and glutathion -S- transferase in normal and profenofos treated rats .

Group	CAT (u/mg protein) Mean ± SD <sup>a</sup>	GST (µmole/h) Mean ± SD <sup>a</sup>
Control	$0.46 \pm 0.029$	$1.42 \pm 0.038$
Control & Cinnamon	$0.49 \pm 0.012$	$1.49 \pm 0.038$
Profenofos	$0.36 \pm 0.029**$	1.04 ± 0.050***
Profenofos & Cinnamon	$0.45 \pm 0.041$	$1.38 \pm 0.022$

a: Results are expressed as mean  $\pm$  SD for four samples

#### Conclusion

From the present results, it can be concluded that commercial processing procedures led to a gradual decrease in the total amount of <sup>14</sup>C-profenofos residues in oils. Also, results obtained indicate that bound <sup>14</sup>C-profenofos residues are highly bioavailable to rats.

The obtained results concluded that exposure of animals to profenofos residues is capable of inducing marked hazardous alterations in most biochemical parameters. Using water extract of cinnamon has capability to alleviate the harmful effect of profenofos residues.

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<sup>\*\*:</sup> Significance at P< 0.02

<sup>\*\*\*:</sup> Significance at P< 0.01

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مصير مبيد البروفينوفوس المرقم بالكربون-١٤ فى بذور وزيوت فول الصويا ، إزالة المتبقيات ، الاتاحة الحيوية ، السمية والتأثير الوقائى لمستخلص نبات القرفة فى حيوانات التجارب

حسن عبد الجواد و حمدى طه قسم الكيمياء العضوية التطبيقية - المركز القومى للبحوث – القاهرة – مصر.

أدى التطبيق الموضعي للبروفينوفوس على نبات فول الصويا إلى ظهور متبقيات في البنور الجافة وصلت إلى ١٠ جزء في المليون في وقت الحصاد بعد المعاملة الثانية . أدت تنقية زيت فول الصويا الخام إلى انخفاض تدريجي في المحتوى الإجمالي لمتبقيات المبيد في الزيوت وقد وصل هذا الانخفاض الى نحو ٨٠٪ من متبقيات المبيد في الزيب الخام لوحظ أنه تم التخلص من جزء كبير من بقايا المبيد بعد تغذية الفئران على الكسب الناتج من عمليات تكرير فول الصويا لمدة الانخلص عن طريق البول والبراز بنسبة ١٨ و ١٢٪ من اجمالي المتبقيات على التخلص عن طريق البول والبراز بنسبة ١٨ و ١٢٪ من اجمالي المتبقيات على التوالي.. تمت دراسة الدور المحتمل للمستخلص المائي للقرفة في التخفيف من الأضرار السمية التي يسببها المبيد في الفئران المعاملة بجرعات متكررة من متبقيات المبيد عن وجود ضرر كبير في الفئران المعاملة وخاصة بالكبد و الكلي و التخلص من معظم هذه الأضرار عن طريق استخدام المستخلص المائي لمسحوق القرفة ومن هذه الأدرارسة يمكن طريق استخدام المستخلصات النباتية المستخدمة لها تأثير مفيد في النقليل من سمية المبيد المستخدم وخاصة في الكبد و الكلي .