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Sub-Acute and Sub-Chronic Effect of Chlorantraniliprole (Coragen® 20% SC) on Albino Rat

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ABSTRACT

Pest control has been achieved by chemical pesticides for more than 70 years but their efficiency is decreased as a result of insecticides resistant problems and environmental concern. The significant increase in pesticide use has increased concerns about potentially adverse effects on human health and the environment. Therefore, alternative insecticides with a new mode of action are needed. The present work aimed to evaluate the toxic effect of the insecticide, chlorantraniliprole (Coragen® 20%SC) on liver and kidney biochemical parameters of albino rats with different sub-acute and sub-chronic doses. The pathological parameters of sub-acute and sub-chronic liver, kidneys and protein profile changes by chlorantraniliprole were assessed. Generally, the tested compound caused a slight decrease in body weight as compared with untreated ones. Also, it caused an increase in AST and ALT activities urea and creatinine. Therefore, a decrease of albumin, globulin and blood calcium content was observed. The present results also clarify our need to avert exposure of humans to chlorantraniliprole and recommend that all pesticides no matter how safe they are must be assessed for their toxicity.

Keywords: Effect, sub-acute, sub-chronic, chlorantraniliprole, Coragen

INTRODUCTION

Globally, Pesticides are often used to combat the problem of the high loss in food production as a result of pest infestation. This problem increased the amount of pesticides used over the past half-century (Chandler, *et al.,* 2011) where we relied solely on theses hazardous chemicals. The use of pesticides has had several benefits including long action, and effective toxicity to a huge species of pests. However, they caused many problems for humans and environment, which encourage researchers to ongoing to find new synthetic pesticides that have high specificity for their target pests and low toxicity to mammals (EPA, 2012a). Therefore, all pesticides no matter how safe they are must be assessed. Diamide insecticides have one of the most favorable new classes of insecticide. The anthranilic diamide, chlorantraniliprole, from DuPont, belongs to insecticide resistance action committee (IRAC) mode of action class 28 (IRAC, 2009). It binds to the ryanodine receptor, which has an important role in controlling the release of calcium stores to the muscles (Kumar, *et al.,* 2013). The flow of $Ca2^{+}$ is interfering in metabolic and physiological cellular processes including; neurotransmission, hormones secretion, and muscles excitation– contraction coupling (Magleby, 1984). The binding leads to reduce the regulation of muscle contraction and causes a unique symptoms including; feeding cessation, lethargy, paralysis, and death (Tohnishi, *et al.,* 2005 – Lahm, *et al.,* 2007 – Lahm, *et al.,* 2009 – Cao,*et al.,* 2010 – Su, *et al.,* 2012). Chlorantraniliprole has an excellent insecticidal efficacy with a very low hazard on mammals (Lahm, *et al.,* 2009). However, subacute oral administration of chlorantraniliprole at 1000 mg/kg body weight for a period of 21 days causes deleterious toxic effect on various haematological parameters in rats (Kumar, *et al.,* 2013). On the other hand, no data are available on oral exposure of chlorantraniliprole, Coragen 20%, at sub-acute and sub-chronic doses. Therefore, the present investigation was undertaken to assess the effect of Coragen 20% on some biochemical parameters in Albino rats at repeated doses, which were administered orally, for a period of 28 and 90 days.

MATERIALS AND METHODS

1. Pesticide and chemicals used

Coragen 20% SC is an anthranilic diamide insecticide containing the active ingredient chlorantraniliprole ($C_{18}H_{14}BrCl_2N_5O_2$). Its CAS chemical name is (3-bromo- *N*- [4- chloro -2- methy l- 6-[(methylamino) carbonyl] phenyl] -1- (3-chloro -2- pyridinyl)- 1*H*-pyrazole -5- carboxamide). Samples of the formulated compound were obtained from central Agriculture Pesticides Laboratory, Agriculture Research Center, Dokki-Giza-Egypt. Analytical reagents (AR)of high purity were used in the subsequent chemical analyses. The oral median lethal dose of Coragn was assessed and calculated according to Weil's method (Weil, 1952) and was found to be 7500mg/kg bw.

2. Experimental Animals

The Sprague- Dawley albino male rats aged 8 weeks, weighing between 120-130 gm were used for sub-chronic toxicity studies .As for sub-acute toxicity studies the albino male rats aged 12 weeks, weighing around 200-230 gm were used. All rats were obtained from National Research Center (NRC), Dokki-Giza, Egypt. The experimental rats were raised in an animal house and kept under laboratory conditions of 25± 2°C, 50 ± 15% RH, and 12:12 (L:D) where free access of water *ad libitum* was allowed. The tested animals were fed on a basal diet consisting of a mixture of casein 20%, cotton seed oil 10%, cellulose 5%, salt mixture

4%, vitamin mixture 1%, and starch 60%, which prepared according to the American Institute of Nutrition instructions (Reeves, *et al.,* 1993). The animals were kept for one week under a health laboratory conditions for adaptation before the initiation of both experiments. In each experiment (sub-chronic and sub-acute) rats divided into four groups (five rats each).

In sub-chronic experiments, the first group was represented by the healthy control animals, while the second, third, and fourth groups were made to orally ingest by gavage sub-lethal doses of Coragen which were 1/20, 1/40, and 1/60 of the oral LD_{50}, respectively. The pesticide was dissolved in water before using. One dose was ingested every two days during the experimental period of 90 days. In sub-acute experiments, the first group was also untreated animals, while the second, third, and fourth groups were made to orally ingest sub-lethal doses of Coragen which were 1/2, 1/4, and 1/6 of the oral LD_{50}, daily by gavage for 28 consecutive days. Body weight was taken on the day of acclimation, before dosing and before scarification. At the end of each experimental period, animals were killed by decapitation for having the blood. Blood samples were divided in two tubes; one in non-heparinized tube for the serum and the 2nd in heparinized tube for plasma. Separating serum and plasma samples were done by centrifugation at 3000 rpm for 10 min, and kept after that, frozen at −20°C until used for analysis. Total soluble protein, albumin and globulin were determined in plasma according to the methods of Bradford (1976) and Doumas *et al.* (1971). Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity were determined by the method of Ritman and Frankel (1957). Urea concentration was determined according to Fawcett and Soctt (1960) while creatinine concentration was determined according to Schrimeister *et al*. (1964) method. Total calcium concentration was analyzed by the colorimetric method according to Connerty and Briggs (1966).

Statistical analyses

The obtained data were expressed as means (±SE), where comparisons were made between treatments using one way ANOVA method (SAS, 2001), and Duncan's multiple range test (Duncan, 1955).

RESULTS AND DISCUSSION

In toxicological studies, toxicants could be transported to various organs where they may cause a harmful effect, that's why a variety of biochemical parameters should be measured to evaluate physi-ological functions affecting organs and tissues injury (Akhtar, *et al.,* 2012). The effects of Coragen sub-acute and sub-chronic toxicity tests on body weight gain are shown in Table (1, 2). In the treatments of sub-acute toxicity, the present results clearly showed that the final body weights and body weight gain were almost the same in control and animals treated with 1/4 and 1/6 LD_{50} of Coragn, while rats which were treated with oral 1/2 of the LD_{50} were slightly lower than those of control in body weights and body weight gain (Table 1).

Body weight gain had decreased in only rats treated with the highest dose, while it was almost the same in all other treated doses. These results agree with those of Wolterink and Dellarco (2008) with mice males at high doses over 28 days.

Sub-chronic toxicity results showed that body weight has decreased in rats that had orally ingested Coragen for 90 days (Table 2). The highest decrease was observed in group of rats treated with 1/20 of the LD_{50}, followed by rats treated with 1/40 of LD_{50} but it was almost the same as the control in animal groups treated with the lowest dose 1/60 of LD_{50}.

Table 1. Effect of chlorantraniliprole (Coragen® 20% SC) sub-acute treatments on body weight gain of albino rat

Treatments	Initial body weight (g)	final body weight (g)	Body weight gain (g)
Control	$220.4^{a} \pm 3.56$	$246.0^{a} \pm 4.21$	$25.60^{a} \pm 1.63$
1/2 LD_{50}	$211.0^{b} \pm 8.62$	$227.7^{b} \pm 10.4$	$16.67^{b} \pm 3.53$
1/4 LD_{50}	$220.0^{a} \pm 3.42$	$247.8^{a} \pm 3.86$	$27.75^{a} \pm 0.63$
1/6 LD_{50}	$210.8^{b} \pm 5.81$	$239.3^{a} \pm 3.71$	$28.67^{a} \pm 2.40$

Table 2. Effect of chlorantraniliprole (Coragen® 20% SC) sub-chronic treatments on body weight gain of albino rat

Treatments	Initial body weight (g)	final body weight (g)	Body weight gain (g)
Control	$125.0^{a} \pm 4.0$	$383.2^{a} \pm 3.26$	$258.0^{a} \pm 3.41$
1/20 LD_{50}	$126.3^{a} \pm 1.892$	$359.8^{b} \pm 2.32$	$236.3^{b} \pm 1.55$
1/40 LD_{50}	$126.8^{a} \pm 3.56$	$371.4^{a} \pm 2.48$	$245.4^{b} \pm 2.11$
1/60 LD_{50}	$123.5^{a} \pm 3.40$	$381.8^{a} \pm 1.94$	$285.3^{a} \pm 1.54$

The present findings could be due to the stress of Coragen chronic poising on the treated rats. Therefore, these results agree with those of Wolterink and Dellarco (2008), who observed significant reductions in the mean body weights and mean body-weight gains in mice male which receive high doses of chlorantraniliprole. In contrast, they noted that these effects were not dose-dependent, and that reduction in body-weight gain was accompanied by a reduction in food efficiency.

In sub-acute treatments, table (3) clearly showed there were no significant changes in kidneys, spleen, brain, heart, muscles and bones weight relative to body weights of animals treated with Coragen compared to untreated ones. Slight but not significant increase in liver weight was observed in animals treated with 1/2, 1/4, and 1/6 of LD_{50} of Coragen. In contrast, testes weight was significantly increased at the tested doses. Nevertheless, table (4) showed that Coragen had no significant changes in brain, heart and muscles weight relative to control in sub-chronic treatments. Liver weight was slightly increased in rats treated with doses corresponding to 1/20, 1/40 of LD_{50}, while kidney weight was slightly decreased at the doses 1/20, 1/40 and 1/60 of LD_{50}. Also, spleen weight was significantly increased in animals which ingested doses equal to 1/20, 1/40 and 1/60 of LD_{50}. Therefore, it can be concluded that the present biochemical changes in treated rats were

dose-dependent. Similar results were obtained by Stebbins (2002) who treated spleen of CD-1 Mice with spinosad. On the other hand, tests weight decreased only in rats ingested 1/20 but there was no significant changes in the doses 1/40 and 1/60 of the LD_{50}. Moreover, bones weight was slightly decreased with the increase of the dose in all of the treated animals. These observations are in part similar to those obtained by the Enivironmental Protection Agency (EPA) (2012b) where no adverse effects were observed, slight increase in liver weight of rats at 128 and 676 mg/kg/day in females and minimal hepatocellular hypertrophy at 675mg/kg/day that is attributed to enzyme induction characterized by increased amount of eosinophilic cytoplasm with hepatocytes but no other histomorphlogic evidence of hepatocellular damage. Also, Coragen had no harmful effects on particular target such as brain, heart and muscles but it had some effect on liver weight in sub-chronic toxicity as stated by the Norwegian Scientific Committee for Food Safety (VKM, 2010). Furthermore, test species such as rats, mice and dogs showed physiological adaptation to chlorantraniliprole administration (increased liver metapolism with induction of cytchrome P 450 enzymes), which was maninfested as increased liver weight and hepatocellular hypertrophy. This accompanied with eosinophilic foci, which was assessed as an adverse effect. In the present study, Coragen decreased the weight of testes however VKM (2010) reported that the potential of testicular toxicity of chlorantranilipore is unclear because the study design and limited number of animal do't provide basis for firm conclusion.

Table 3. Effect of chlorantraniliprole (Coragen®20% SC) sub-acute treatments on organs weight of albino rat

Treatments	final body weight (g)	Liver Weight (g)	Ratio	Kidney Weight (g)	Ratio	Brain Weight (g)	Ratio	Heart Weight (g)	Ratio	Spleen Weight (g)	Ratio	Tests Weight (g)	Ratio	Muscles Weight (g)	Ratio	Bones Weight (g)	Ratio
Control	246.0^{a} ± 4.21	2.80^{a}± 0.09	1.14	0.80^{a}± 0.08	0.32	0.75^{a}± 0.04	0.30	0.29^{a}± 0.04	0.12	0.31^{a}± 0.18	0.13	0.93^{b}± 0.064	0.40	4.59^{a}± 0.23	1.87	2.49^{a}± 0.40	1.01
1/2 LD_{50}	227.0^{b} ± 10.40	3.10^{a}± 0.64	1.37	0.84^{a}± 0.04	0.37	0.76^{a}± 0.05	0.33	0.30^{a}± 0.07	0.13	0.29^{a}± 0.01	0.13	1.21^{a}± 0.13	0.53	4.58^{a}± 0.417	2.02	2.33^{a}± 0.31	1.03
1/4 LD_{50}	247.8^{a} ± 3.86	2.98^{a}± 0.60	1.21	0.65^{a}± 0.12	0.26	0.76^{a}± 0.02	0.30	0.32^{a}± 0.03	0.13	0.28^{a}± 0.03	0.12	1.05^{ab} ± 0.06	0.44	4.56^{a}± 0.29	1.58	2.33^{a}± 0.36	0.94
1/6 LD_{50}	239.3^{a}± 3.71	3.07^{a}± 0.12	1.28	0.66^{a}± 0.12	0.27	0.81^{a}± 0.06	0.33	0.29^{a}± 0.03	0.12	0.28^{a}± 0.35	0.12	1.29^{a}± 0.04	0.53	4.64^{a}± 0.45	1.93	2.44^{a}± 0.19	1.02

Values marked with different letters within the same column are significantly different (P > 0.05: Duncan's multiple range test)

Table 4. Effect of chlorantraniliprole(Coragen®20%SC)sub-chronic treatments on organs weight of albino rat

Treatments	final body weight (g)	Liver Weight (g)	Ratio	Kidney Weight (g)	Ratio	Brain Weight (g)	Ratio	Heart Weight (g)	Ratio	Spleen Weight (g)	Ratio	Tests Weight (g)	Ratio	Muscles Weight (g)	Ratio	Bones Weight (g)	Ratio
Control	383.2^{a} ± 3.26	4.21^{a}± 0.23	1.1	1.04^{a}± 0.08	0.27	1.50^{a}± 0.10	0.39	0.49^{a}± 0.13	0.13	0.63^{c}± 0.05	0.16	1.73^{a}± 0.23	0.44	6.18^{a}± 0.36	1.61	3.85^{a}± 0.48	1.00
1/20 LD_{50}	359.8^{b} ± 2.32	5.88^{a}± 0.20	1.63	0.79^{b}± 0.19	0.22	1.39^{a}± 0.05	0.38	0.43^{a}± 0.07	0.12	1.41^{a}± 0.03	0.39	1.01^{b}± 0.11	0.28	6.00^{a}± 0.70	1.67	2.55^{a}± 0.10	0.72
1/40 LD_{50}	371.4^{a} ± 2.48	5.39^{a}± 0.24	1.45	0.78^{b}± 0.02	0.21	1.41^{a}± 0.04	0.38	0.43^{a}± 0.06	0.12	1.05^{b}± 0.02	0.28	1.50^{a}± 0.10	0.40	6.12^{a}± 0.42	1.64	2.93^{a}± 0.24	0.79
1/60 LD_{50}	381.8^{a} ± 1.94	4.13^{a}± 0.16	1.08	0.77^{b}± 0.13	0.20	1.40^{a}± 0.04	0.37	0.51^{a}± 0.08	0.13	0.75^{c}± 0.02	0.19	1.84^{a}± 0.15	0.48	6.14^{a}± 0.37	1.61	3.62^{a}± 0.20	0.95

Values marked with different letters within the same column are significantly different (P > 0.05: Duncan's multiple range test)

On the other hand, bones weight of treated rats with Coragen was slightly decreased. Bones weight of treated Coragen rats were slightly decreased and that may be due to Coragen mode of action which binds and activates ryanodine receptors, resulting in depletion of intracellular calcium stores which may affect calcium storage in bones. Table (5) summarizes the sub-acute toxicity of Coragen on some biological parameters such as AST, ALT, total protein, albumin, globulin, urea and creatinine in treated rats. Coragen ingestion had a significant effect on the AST activity, which gradually increased with increasing of Coragen doses till it reached the highest levels in rates treated with the 1/2 of LD_{50} dose. Similar trend of observations was noticed with ALT enzyme where its activity was significantly elevated in the group of animals treated with 1/2 of LD_{50} dose. Moreover, protein profile of plasma was changed under ingestion of Coragen in sub-acute toxicity experiments as shown in Table (5). The results clearly showed a slight reduction in total soluble protein, albumin and globulin. Also, sub-acute Coragen treatment stimulated plasma contents of urea while creatinine was not affected.

In the case of Coragen sub-acute toxicity treatments, liver parameters including AST and ALT activities were used to check hepatotoxicity in intoxicated animals. It was found that Coragen had significant effects on AST activity especially when

Coragen ingested doses were increased. That means the stimulations were found to be dose dependent. While there was a significant increase in ALT enzyme only in rats which were previously exposure to the highest dose but all other doses remain the same to as the untreated control. These results showed that the variation in total protein of plasma was correlated with the changes in albumin values. This may be due to the inhibition of albumin biosynthesis through specific enzymes in cell processes and low significant excretion of hormones which regulate protein biosynthesis.

Table 5. Effect of chlorantraniliprole (Coragen® 20% SC) sub-acute treatments on liver and kidney functions of albino rat

Treatments	Total protein g/dl	Ratio %	Albumin g/dl	Ratio %	Globulin g/dl	Ratio %	AST activity U/l	Ratio %	ALT activity U/l	Ratio %	Urea (mg/dl)	Ratio %	Creatinine (mg/dl)	Ratio %
Control	$8.61^{a}\pm$ 0.21	100	$2.67^{a}\pm$ 0.21	100	$5.94^{a}\pm$ 0.22	100	62.97^{c} ± 0.96	100	40.80^{c} ± 0.81	100	29.23^{c} ± 0.26	100	0.35^{a} ± 0.006	100
1/2 LD_{50}	$5.34^{d}\pm$ 0.13	62.02	$2.09^{a}\pm$ 0.05	78.28	$3.25^{c}\pm$ 0.5	54.71	87.48^{a} ± 1.63	138.9	56.95^{a} ± 2.06	139.5	44.01^{a} ± 0.58	150.5	0.46^{a} ± 0.017	131.4
1/4 LD_{50}	$6.29^{c}\pm$ 0.08	73.05	$2.52^{a}\pm$ 0.06	94.38	$3.77^{c}\pm$ 0.05	63.47	83.44^{a} ± 2.03	132.5	46.92^{b} ± 1.07	155	43.59^{a} ± 0.36	149.1	0.40^{a} ± 0.002	114.2
1/6 LD_{50}	$7.07^{b}\pm$ 0.26	82.11	$2.45^{a}\pm$ 0.05	91.7	$4.62^{b}\pm$ 0.16	77.78	80.99^{b} ± 3.43	128.6	46.15^{b} ± 0.40	113.1	30.68^{b} ± 0.66	102.6	0.39^{a} ± 0.005	111.4

Values marked with different letters within the same column are significantly different (P > 0.05: Duncan's multiple range test)

Urea and creatinine values were only stimulated in the rats ingested the highest doses of Coragen, but rats treated with the other doses were almost normal. These findings agree with what was found when the effect of short term toxicity studies on mice and rats were investigated an induction of liver enzymes with subsequent increase in liver weight were recorded (EPA, 2010b). Dutta, *et al*. (2014) observed a significant increase in urea and creatinine levels which are a classical sign that the kidney was adversely affected by Coragen administration. Also, Saafi-Ben Salah, *et al*. (2012) reported that oral administration of pesticides in rats induced a marked renal failure characterized by a significant increase in serum urea levels.

Table (6) summarizes the effect of Coragen sub-chronic toxicity treatment on AST, ALT, total protein, albumin, globulin, urea and creatinine. The present results showed that Coragen ingestion stimulated AST and ALT, The stimulation was gradually paralleled with the increasing of Coragen ingested doses, until it reached the highest value at 1/20 LD_{50} treatment. Protein profile of plasma was significantly changed where a significant reduction in total soluble protein, albumin and globulin values were noticed decreased in animal groups treated with 1/20 of the LD_{50} of Coragen. Also, urea was significantly increased by all doses especially at 1/20 of the LD_{50}, however in case of creatinine, no significant changes were observed where creatinine was almost remaining stable in all sub-chronic intoxicated rats.

Table 6. Effect of chlorantraniliprole (Coragen® 20% SC) sub-chronic treatments on liver and kidney functions of albino rat

Treatments	Total protein g/dl	Ratio %	Albumin g/dl	Ratio %	Globulin g/dl	Ratio %	AST activity U/l	Ratio %	ALT activity U/l	Ratio %	Urea (mg/dl)	Ratio %	Creatinine (mg/dl)	Ratio %
Control	$8.12^{a}\pm$ 0.45	100	$4.41^{a}\pm$ 0.11	100	$3.17^{b}\pm$ 0.15	100	61.43^{d} ± 1.11	100	37.74^{c} ± 0.48	100	49.74^{d} ± 0.47	100	0.50^{b} ± 0.007	100
1/20 LD_{50}	$5.76^{b}\pm$ 0.17	70.94	$3.60^{b}\pm$ 0.08	81.63	$2.16^{c}\pm$ 0.2	68.14	87.75^{a} ± 0.10	142.8	50.91^{a} ± 0.76	134.9	71.80^{a} ± 0.70	124.1	0.56^{a} ± 0.027	112
1/40 LD_{50}	$8.31^{a}\pm$ 0.11	102.3	$4.17^{a}\pm$ 0.15	94.56	$4.14^{a}\pm$ 0.11	130.6	80.66^{b} ± 1.43	131.3	48.91^{a} ± 1.07	130.5	58.17^{b} ± 2.10	116	0.56^{a} ± 0.008	112
1/60 LD_{50}	$8.18^{a}\pm$ 0.16	100.7	$4.15^{a}\pm$ 0.12	94.10	$4.03^{a}\pm$ 0.09	127.1	73.28^{c} ± 1.31	119.3	41.36^{b} ± 1.48	109.5	55.21^{c} ± 0.37	112	0.52^{ab} ± 0.008	104

Values marked with different letters within the same column are significantly different (P > 0.05: Duncan's multiple range test)

The studies of biochemical parameters have a significant value in toxicological evaluations because their alternations appeared quite before the clinical symptoms which produced by the toxicant (Evans, 1996). Several studies were conducted to evaluate the haemotological biochemical changes induced by pesticides on rats (Ayse *et al.,* 2008; Saafi-Ben Salah, *et al.,* 2012; Salim *et al.,* 2014 and Kingsley *et al.,* 2016). The liver is well known as the organ most commonly involved in the metabolism of endogenous and foreign compounds. Therefore, liver enzymes such as AST and ALT which are frequently used as biomarkers of liver injury, that because they are released by hepatocytes into extracellular space (El-Shenawy and Abdel-Rahman, 1963; Pari and Kumar, 2002; Ozer, *et al.,* 2008 and El-Sayed, 2012). The significant increase in AST and ALT values, which were obtained in this study, indicated that the Coragen formulation is possibly

hepatoxic. These findings agree earlier observations of Dutta *et al.* (2014) who found that Coragen caused severe hepatoxicity.

Protein profile was significantly decreased only in the rats treated with the highest dose 1/20 of LD_{50}. Similar results were obtained with albumin and globulin. These results are in agreement with those of the Australian Pesticdes and Vetrinary Medicines Authority (APVMA) (2009) which showed that diamide insecticides decreased albumin and the albumin/globulin ratio at and above 1500 ppm when flubendiamide was tested on rats' male in sub-chronic and chronic studies.

Creatinine and blood urea are typically used to diagnose kidney injury (Edelstein, 2008). The present studies showed some increase in blood urea levels with the sub-chronic Coragen ingestion (Table 6). However, there were no observed effects on creatinine concentrations in all treated animal groups. Such elevation of urea levels may be attributed to some reduction in glomerular filtration in the animal kidneys. The increase of urea levels may be a demonstration of impaired kidney function since it is the organ that excretes urea in the urine (Walmsley and White, 1994).

Also, the present investigations proved that Coragen affected serum calcium content in both sub-acute and sub- chronic toxicity treatments as shown in Figs 1 and 2. A slight decrease of calcium content in serum was observed in sub-acute treated rats and the highest toxicity effects occurred in rats receiving 1/2 of the LD_{50} (Fig. 1). Also, in chronic treatments, significant decreases were observed in serum calcium content, where the highest decrease was found in rats receiving 1/2 of the LD_{50} followed by 1/4 and 1/6 of the LD_{50} dose, respectively (Fig 2).

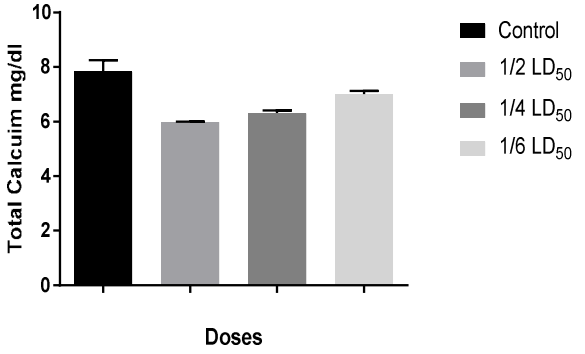

Fig. 1. Effect of chlorantraniliprole (Coragen® 20% SC) sub-acute treatments on serum calcium content on albino rat.

The decrease of calcium serum content may be due to the mode of action of Coragen, which acts by activating the ryanodine receptors (RyRs), it stimulates the release and depletion of intracellular calcium stores from the sarcoplasmic reticulum of muscle cells, causing impaired muscle regulation, paralysis and ultimately death of sensitive species (Cordova *et al.,* 2006). The results also showed that there was a positive correlation between albumin and calcium levels I serum of treated animals. Therefore, the reduction of calcium level may be due to the decrease of albumin level. These findings are supported by the results of Garniasih (2008) who found a relationship between serum albumin and calcium in children with Nephrotic syndrom. Moreover, the present results are in harmony with those of Meuten *et al.* (1982) who noted a positive linear relationship between total calcium and albumin and between total calcium and total protein in blood serum of dogs. Also, it was previously reported that dogs received doses of flucythrinate had remarkable desperation of calcium and albumin levels (Fao, 1985).

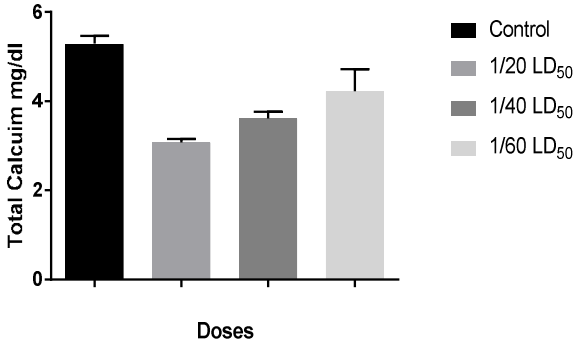

Fig. 2. Effect of chlorantraniliprole (Coragen® 20% SC) sub-chronic treatments on serum calcium content on albino rat.

CONCLUSION

In conclusion, the study showed the pathological parameters of sub-acute and sub-chronic liver, kidneys and protein profile changes by Coragen (chlorantraniliprole), which caused increases in AST and ALT activities, urea and creatinine concentrations. Also, a decrease of albumin, globulin and blood calcium content was observed. The results of the present work advice the need to avoid exposure of humans to Coragen and recommend that all pesticide no matter how safe it is must assess its toxicity.

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التأثير تحت الحاد وتحت المزمن للكلورانترانيليبرول (كوراجين٢٠%) على الفأر الأبيض

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بدأت مكافحة الآفات الزراعية باستخدام المبيدات الكيميائية منذ أكثر من ٧٠ عاماً. ولكن حديثاً انخفض نسبيا استخدام تلك المبيدات كنتيجة لكثير من المشاكل التي نجمت من استمرارية والإفراط وسوء استخدامها مثل التلوث البيئي وزيادة المخاوف بشأن الآثار الضارة المحتملة على صحة الإنسان. لذلك كانت هناك حاجة ملحة لاستنباط مبيدات بديلة أكثر أماناً مع أسلوب متطور في العمل. ويهدف هذا البحث إلى تقييم التأثير السام للمبيد الحشري الحديث كلورانترانيليبرول (Coragen® 20٪) على الفأر الأبيض. أوضحت النتائج إنخفاض طفيف في وزن الفئران المعاملة مقارنة بالفئران غير المعاملة. كذلك سجلت النتائج زيادة في نشاط إنزيمي إسبرتيتأمينو ترانس فريز (AST) و آلانين أمينوترانس فريز (ALT) وفي نسبة كل من اليوريا والكرياتينين. كما أظهرت النتائج إنخفاض مستوى الألبيومين والجلوبيولين بالإضافة إلى إنخفاض محتوى الدم من الكالسيوم. كما لوحظ أن المعاملة بالجرعات تحت الحادة والمزمنة من هذا المبيد لم يكن لها تأثير معنوي على وزن كل من الكلى والطحال والمخ والقلب والعضلات والعظم في الفئران المعاملة وعلى العكس من ذلك فقد سجلت زيادة معنوية في وزن الخصى في الفئران المعاملة