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TOXICOLOGICAL STUDIES WITH THE ANTICOAGULANTS, BRODIFACOUM AND DIFENACOUM ON MICE

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ABSTRACT

The effect of two dose levels of brodifacoum and difenacoum on some hematological and biochemical targets of male and female mice after 24 and 72 hours of treatments was studied. The data obtained showed that the red blood cells count (RBC's) decreased slightly in male and female mice treated with 1/4 LD_{50} of brodifacoum or difenacoum, while the higher dose (LD_{50}) induced highly significant reduction. In contrast, the white blood cells count (WBC's) increased. Also the higher dose induced marked decreased in hemoglobin content (Hb) and hematocrit value (Hct). The prolongation in prothrombin time (PT) and partial thromboplastin time (PTT) was extended by increasing the dose level and reached their maximum values at the third day after treatment. The activity of liver aniline hydroxylase was significantly increased in treated mice. Brain adenosine triphosphatase (ATPase) increased after the same treatment, while liver ATPase was not changed significantly. Brodifacoum stimulated the activity of liver acid phosphatase (APase). Kidney APase slightly decreased in all treatments. Difenacoum did not induce a change in liver APase and glutamate oxaloacetate transaminase (GOT).

The changes of the electrophoretic patterns of male mice plasma proteins treated with brodifacoum may be due to the dose levels or time elapsed after treatment; such changes were not

markedly noticeable in female mice.

INTRODUCTION

Rodents have become a great social problem, in almost all the countries of the world. They are extremely damaging to a wide variety of human interests. In addition, rodents are involved in the transmission of more than 20 disease organisms. Despite the fact that chemical control of rodents has been practised form more than 2000 years (Dubock, 1979), it was only about 50 years ago that the introduction of anticoagulant rodenticides revolutionized the efficacy and safety of chemical control of rodents. The discovery of resistance to warfarin led directly to the development of two new anticoagulants, brodifacoum and difenacoum, which are highly effective against rodents (Brooks, et al. 1980, and Lund, 1981). In Egypt, anticoagulant rodenticides are used on a large scale to control rodents in agriculture as well as for public health purposes. The possibility of such compounds reaching the food of non-target animals or even human beings, prompted us to study the side effects of such compounds in order to give a clear idea about the physiological disturbances which may occur on the exposure of non-target animals or human subjects to such anticoagulants. The present study aims at assessing the effects of two commonly used anticoagulants (brodifacoum and difenacoum) on some biochemical and hematological targets in the tested mice, under different stressful conditions. Interpretation of the data may help in rodent control and protection of the occupationally exposed workers or the surrounding livestock.

MATERIALS AND METHODS

Tested Animals

Male and female albino mice strain (Mus musculus) weighing 25-30 gm were used in this

study. They were taken from the High Institute of Public Health, Alexandria University.

Rodenticides Used

Technical materials (96.8%) from brodifacoum, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy coumarin; and difenacoum, 3-[3-(1,1'-biphenyl) 4-yl-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy coumarin were used. The doses administered in this study were 0.1 and 0.4 mg/kg from brodifacoum and 0.2 and 0.8 mg/kg from difenacoum. These doses represented the 1/4 LD_{50} and LD_{50} of each compound according to Worthing and Walker (1983).

Animal Treatments

Four groups of male and four groups of female mice were orally treated with 1/4 LD_{50} and LD_{50} of brodifacoum and difenacoum. The fifth groups was treated with corn oil and used as control. Five male and female mice from each group were decapitated after 24 and 72 hours of treatment. Blood was collected from each animal in citrated tubes. Livers and brains were removed quickly and stored frozen.

Hematological Tests

Fresh blood samples were used without delay. RBC's and WBC's counts were carried out using the hemocytometer. Hemoglobin content was determined by a colorimetric method (Drabkin and Austin, 1932) using a commercial reagent of Bio-Merieux Company. Hematocrit percent was measured using hematocrit centrifuge (MLW-TH-21). Plasma was used for determination of prothrombin time and partial thromboplastin time as described by Dacie and Lewis (1984) by using a Behring Company kit.

Enzyme Activities Determination

Brain, liver and kidney samples were homogenized in ice cold physiological saline

solution, 0.9%, then centrifuged at 8,000 xg for 20 minutes. The supernatant was used for determination of aniline hydroxylase, ATPase, APase and GOT. The activity of liver aniline hydroxylase dependent the formation of p-aminophenol from aniline, using the colorimetric method described by Imai, et al. (1966). Activities of ATPase in liver and brain were determined according to Koch, et al. (1969). APase was measured in liver and kidney using the method of Bessey, et al. (1946). Liver GOT was assayed colorimetrically according to Reitman and Frankel (1957). Estimation of protein concentration was done by the method of Lowry, et al. (1951).

Plasma Protein Fractionation

The sodium-dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was performed as described by Laemmli (1970). Plasma samples were prepared from control and treated mice with 1/4 LD_{50} and LD_{50} of brodifacoum after 24 and 72 hours of treatment for both male and females. Five µl of plasma samples were loaded into each lane of 10% acrylamide slab gel in the absence of reducing agent. Gel was stained using Coomassle blue R250.

Statistical analysis is done using student's t-test to compare between each group and control.

RESULTS AND DISCUSSION

I. Effect of Brodifacoum and Difenacoum on the Hematological Parameters in Mice.

In the present investigation, the effect of two concentrations of brodifacoum (0.1 and 0.4 mg/kg) and difenacoum (0.2 and 0.8 mg/kg) on the RBC, WBC, hemoglobin and hematocrit in male and female mice was evaluated (Tables 1 and 2). It was noticed that RBC's count slightly decreased in male mice treated with 1/4 LD_{50} of brodifacoum or difenacoum after 24 and 72 hours, while the

Table 1

Hematological Studies on Male Mice Treated with 1/4 LD_{50} and LD_{50} of Brodifacoum and Difenacoum After 24 and 72 Hours.

Treatment	Hrs post-treatment	Hematological and coagulation parameters (mean ±SD) RBC's count $x10^6/\mu l$	WBC's count $x10^3/\mu l$	Hb content g/dl	Hct. value %	Pt seconds	PTT seconds
Control		7.95 ±1.70	6.83 ±1.45	14.26 ±1.97	42.65 ±2.61	6.50 ±2.10	24.50 ±1.20
Brodifacoum							
1/4 LD_{50}	24	7.25 ±0.15	6.50 ±0.87	13.83 ±0.87	39.67 ±3.39	8.5 ±0.35	26.00 ±1.20
	72	6.66 ±1.70	7.95 ±0.50*	13.39 ±0.93	41.00 ±3.2	12.25 ±0.35*	35.50 ±2.10*
LD_{50}	24	4.44 ±0.65*	7.45 ±1.01*	6.96 ±1.80*	18.72 ±0.87*	80.00 ±2.3*	150.00 ±4.1*
	72	3.610 ±0.5*	8.35 ±1.27*	5.39 ±0.98*	15.50 ±1.5*	180 ±1.56*	380.00 ±5.1*
Difenacoum							
1/4 LD_{50}	24	7.63 ±3.10	6.92 ±1.90	13.47 ±0.46	40.0 ±3.90	7.60 ±2.02	25.34 ±1.52
	72	6.90 ±1.70	7.76 ±0.65*	13.14 ±0.67	39.6 ±2.23	18.05 ±3.02*	28.40 ±1.52*
LD_{50}	24	5.93 ±0.07*	7.72 ±1.53*	8.53 ±1.00*	24.33 ±1.16*	90 ±2.51*	210 ±2.10*
	72	4.85 ±0.05*	8.10 ±0.78*	7.17 ±0.81*	21.0 ±2.56*	150 ±3.45*	210 ±5.1*

* : Significant change from control at $P < 0.05$

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Table 2

Hematological Studies on Female Mice Treated with 1/4 LD_{50} and LD_{50} of Brodifacoum and Difenacoum After 24 and 72 Hours.

Treatment	Hrs post-treatment	Hematological and coagulation parameters (mean ±SD) RBC's count $x10^6/\mu l$	WBC's count $x10^3/\mu l$	Hb content g/dl	Hct. value %	Pt seconds	PTT seconds
Control		7.35 ±0.22	6.80 ±0.98	13.74 ±0.20	39.00 ±3.05	6.75 ±1.48	22.00 ±2.3
Brodifacoum 1/4 LD_{50}	24	7.19 ±0.62	6.78 ±0.32	12.95 ±0.49	37.5 ±3.54	10.50 ±1.0*	25.40 ±0.89*
	72	7.03 ±0.08	7.75 ±0.49	10.65 ±0.25	38.25 ±2.47	11.32 ±5.42*	28.00 ±21.39*
LD_{50}	24	3.50 ±0.12*	7.73 ±1.17	5.56 ±0.17*	16.00 ±1.34*	65.67±11.47*	130.00±377.10*
	72	2.19 ±0.23*	8.70 ±2.05*	3.57 ±0.12*	14.52 ±2.13*	106.50±10.92*	375.00±318.20*
Difenacoum 1/4 LD_{50}	24	7.03 ±1.05	7.75 ±0.39	13.69 ±0.67	38.15 ±2.11	8.50 ±2.50*	28.00 ±2.80*
	72	7.82 ±2.50	7.60 ±2.50	10.33 ±1.50	37.00 ±2.50	9.00 ±1.50*	30.00 ±2.51*
LD_{50}	24	5.20 ±1.09*	7.40 ±0.54	8.86 ±2.30*	25.00 ±3.91*	25.33 ±2.33*	120.00 ±3.46*
	72	4.23 ±1.80*	8.35 ±0.53	7.23 ±3.20*	20.00 ±4.87*	63.50 ±2.75*	150 ±6.01*

* : Significant change from control at $P < 0.05$

higher doses (LD_{50}) of brodifacoum and difenacoum induced highly significant reduction, 54.6% and 39%, respectively, in erythrocytic count compared with untreated male mice. The WBC's count increased in contrast to the red ones. The high increase of leucocytes may be due to the inflammatory response induced as a defence mechanism. Hemoglobin contents (gm/100 ml blood) in male mice treated with 1/4 LD_{50} of either brodifacoum or difenacoum were not significantly different at any time after the treatment as compared with that of their control group of mice. In contrast, the concentration of hemoglobin was markedly decreased in treated male mice with LD_{50} of brodifacoum and difenacoum, reach to 5.39 and 7.17 g/dl, respectively, after 72 hours of treatment compared with untreated mice (14.26 g/dl). The results obtained in case of female mice (Table 2) were nearly the same as male mice in these respects.

The reduction in the hemoglobin content, together with the decreased erythrocytes count explains the drop in the hematocrit values recorded in the present study. The decrease in hematocrit and hemoglobin values may also point to hydration, anaemia and transfusion of fluid after bleeding. These results are in full agreement with the results of Helal, et al. (1975); El Mahrouki (1984); Ahmed, et al. (1989); Shimaila (1989), and Said (1990).

II. Effect of Brodifacoum and Difenacoum on Blood Coagulation in Mice.

The effect of brodifacoum and difenacoum at the two dose levels on the coagulation process of the blood was assessed by measuring the prothrombin time (PT) and the partial thromboplastin time (PTT). The PT and PTT assays are valuable in the study of hemostatic disorders of animals, as well as people. PT and PTT are used to test the disorders of extrinsic and intrinsic pathways of blood coagulation, respectively. Table 1 shows that the

prolongation in PT and PTT is extended by increasing the dose level and reached their maximum values at the third day after treatment, i.e. 180 and 360 seconds for LD_{50} brodifacoum treatment, and 150 and 210 seconds for LD_{50} difenacoum treatment. While the PT and PTT of male mice treated with 1/4 LD_{50} of both compounds show little increas. The prolonged PT and PTT were also previously recorded in rats treated with anticoagulant by Ahmed, et al., (1989) and Said (1990). These results show that the high dose from both compounds exhibited severe hypoprothrombinaemia and complete blocking of the clotting factors activity and this effect was detected after 24 and 72 hours of treatment. The results tabulated show that the effect of the anticoagulants increased by increasing the concentrations and/or by lengthening the time after treatment; hence after 72 hours the effect was more potent than that after 24 hours. Also it shows that brodifacoum is more effective than difenacoum. Similar results were noticed in female, as well as in male mice with insignificantly higher response in female groups.

III. Effect of Brodifacoum and Difenacoum on Some Biochemical Responses of Mice

This part of the study is performed to illustrate the effects of two dose levels of brodifacoum and difenacoum on some enzymes (aniline hydroxylase, ATPase, APase and GOT) in liver, kidney or brain of both male and female mice after 24 and 72 hours. Data in Tables 3 and 4 show that the specific activity of liver aniline hydroxylase is significantly increased in treated mice compared with untreated ones. The induction in treated mice with LD_{50} of brodifacoum and difenacoum after 72 hours reaches to 1.38 and 1.16 times in male mice and to 1.85 and 1.83 times in female mice, respectively. It is clear that the percentage induction is more in treated females than in males. On the other hand, brodifacoum stimulated aniline hydroxylase more than difenacoum. Also, the percentage

Table 3

Effect of 1/4 LD_{50} and LD_{50} of Brodifacoum and Difenacoum on Some Enzymes of Male Mice After 24 and 7[illegible] Hours.

Treatment	Hours post treatment	Aniline hydroxylase µmole/min/gm liver	ATPase µmole Pi/mg protein/hr liver	ATPase µmole Pi/mg protein/hr brain	APase µmole p-nitrolphenol/ mg protein/min liver	APase µmole p-nitrolphenol/ mg protein/min kidney	GOT µ/gm liver
Control		116.25 ±2.89	1.97 ±0.23	2.69 ±0.23	3.62 ±1.08	3.22 ±0.82	11.59 ±2.47
Brodifacoum 1/4 LD_{50}	24	124.61±4.41	2.11 ±0.38	2.89 ±0.19	4.70 ±0.23*	2.79 ±0.77	9.35 ±1.09
	72	130.96±2.2	2.12 ±0.14	2.99 ±0.12	3.99 ±0.60	2.52 ±0.28	8.55 ±1.25
LD_{50}	24	149.31±10.46*	1.98 ±0.19	3.40 ±0.07*	4.08 ±0.52*	2.73 ±0.80	8.74 ±1.7
	72	160.23±7.32*	2.25 ±0.35	3.55 ±0.07*	3.67 ±0.52	2.31 ±0.16	8.83 ±0.30
Difenacoum 1/4 LD_{50}	24	122.32±49.44	2.07 ±0.14	3.32 ±0.16*	3.08 ±0.38	2.90 ±0.34	12.65 ±0 87
	72	124.07±83.70	2.16 ±0.40	3.46 ±0.28*	3.46 ±0.29	2.79 ±0.57	11.65 ±0.87
LD_{50}	24	132.4±44.85*	2.19 ±0.018	3.95 ±0.37*	3.10 ±1.34	2.64 ±0.48	11.99 ±0.27
	72	135.25±5.76*	2.25 ±0.15	3.38 ±0.32*	3.44 ±0.22	3.03 ±0.52	12.83 ±0.71

* : Significant change from control at $P < 0.05$

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Table 4

Effect of 1/4 LD_{50} and LD_{50} of Brodifacoum and Difenacoum on Some Enzymes of Female Mice After 24 and 72 Hours.

Treatment	Hours post treatment	Aniline hydroxylase µmole/min/gm liver	ATPase µmole Pi/mg protein/hr liver	ATPase µmole Pi/mg protein/hr brain	APase µmole p-nitrolphenol/, mg protein/min liver	APase µmole p-nitrolphenol/, mg protein/min kidney	GOT µ/gm liver
Control		106.01±7.43	1.04 ±0.52	3.22 ±1.02	3.70 ±0.93	3.33 ±0.87	13.99 ±0.33
Brodifacoum							
1/4 LD_{50}	24	114.17±5.76	1.00 ±0.025	4.01 ±0.39*	4.45 ±1.15*	2.42 ±0.40	12.57 ±1.73
	72	125.43±2.06*	0.98 ±0.028	4.29 ±0.43*	4.80 ±0.25*	2.78 ±0.20	12.83 ±1.93
LD_{50}	24	191.65±3.23*	0.99 ±0.01	5.12 ±0.31*	4.70 ±0.14*	2.67 ±0.64	10.94 ±1.38
	72	195.64±1.69*	0.96 ±0.09	5.95 ±0.21*	4.16 ±1.14*	3.61 ±0.20	9.90 ±1.09
Difenacoum							
1/4 LD_{50}	24	110.36±5.66	0.98 ±0.083	4.30 ±1.36*	3.23 ±0.66	2.77 ±0.37	13.41 ±0.50
	72	124.01 ±4.72*	1.02 ±0.16	4.93 ±0.61*	3.15 ±0.24	3.24 ±0.32	14.75 ±0.23
LD_{50}	24	176.11 ±2.45*	1.05 ±0.12	4.84 ±1.1*	3.16 ±0.37	2.10 ±0.76	14.28 ±0.94
	72	194.17±2.26*	1.28 ±0.32	5.90 ±0.81*	3.49 ±0.22	3.03 ±0.04	13.97 ±1.15

* : Significant change from control at $P < 0.05$

induction of the enzyme is increased by the dose level and by the time elapsed after the treatment. These results are in agreement with Casterline and Clara (1971), and Shimaila (1989).

Total ATPase activity was measured in liver and brain. The data shows that the activity of ATPase is higher in brain than in liver of the teated male and female mice. There is no significant difference noticed in liver ATPase treated with two dose levels of brodifacoum or difenacoum, either in male or female mice. The brain ATPase activity is stimulated in male and female mice with 1.26 and 1.85 folds in LD_{50} brodifacoum and difenacoum treatments, respectively, after 24 hours of administration. These results are parallel to Ramarchandra Pai, et al. (1975) and Ahmed, et al. (1989), who found that the brain ATPase activity increased in treated rat with anticoagulant compounds. Kidney and liver are chosen to evaluate the in vivo effects of 1/4 LD_{50} and LD_{50} of brodifacoum and difenacoum on mice acid phosphatase because they contained the highest activities (Moss, et al., 1987; and El-Gendy, et al., 1990). The results obtained reveal that brodifacoum increases the activity of liver APase after 24 and 72 hours in both male and female mice, while there is no difference observed in difenacoum treated mice. Kidney APases are slightly decreased in treated mice with both anticoagulant compounds.

Transaminases are important and critical enzymes in the biological processes. It is clear that brodifacoum slightly reduces the activity of liver GOT in both male and female mice, while difenacoum does not affect it. From previous investigators it was noticed that different pesticides had oscillating effects on GOT activity activation (Rojik, et al., 1983), inhibition (Enan, et al., 1982) or no effect (Ahmed, et al., 1983).

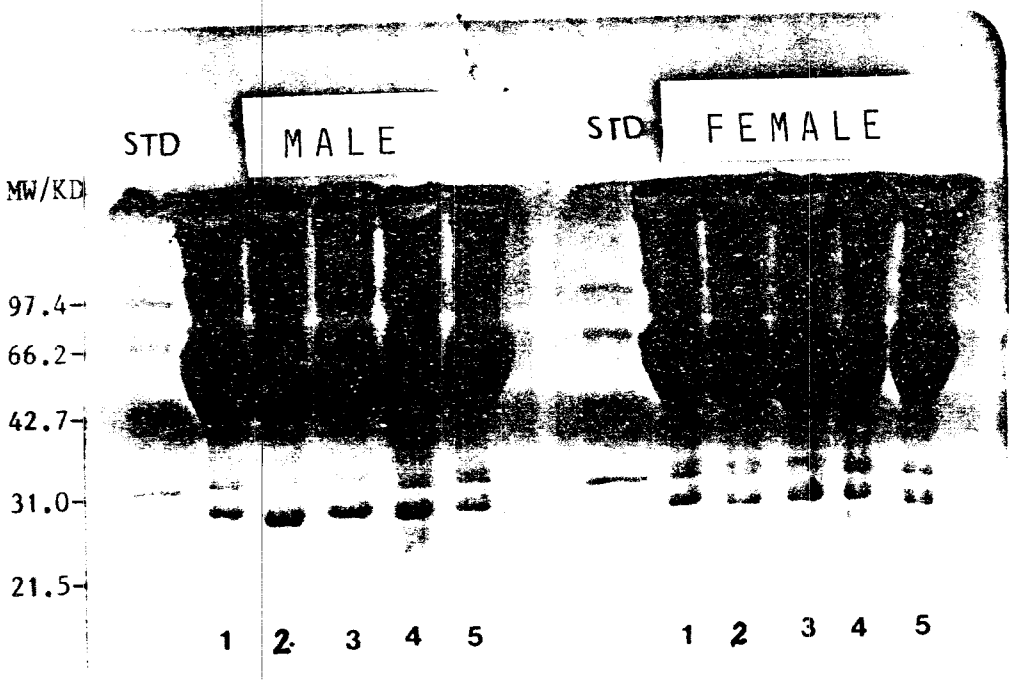

Fig (1): SDS-PAGE of plasma protein; from male and female mice treated with brodifacoum.

Lane 1 : The Control

Lane 2 : $\frac{1}{4}$ LD_{50} of brodifacoum after 24 hours.

Lane 3 : $\frac{1}{4}$ LD_{50} of brodifacoum after 72 hours.

Lane 4 : LD_{50} of brodifacoum after 24 hours.

Lane 5 : LD_{50} of brodifacoum after 72 hours.

STD : Low molecular weight standard protein .

IV. Plasma Protein Fractions

Figure 1 presents the electrophoretic patterns of plasma proteins of control and treated male and female mice with 1/4 LD_{50} and LD_{50} of brodifacoum after 24 and 72 hours. It is clear that the color intensity of the band at about 28 KD was increased in lanes 2 to 4 in males, when compared with control. It is also interesting to note that the color of the band at about 31 KD of lane 2 and 3 (1/4 LD_{50} of brodifacoum after 24 and 72 hours) of both male and females was reduced more than the other treatments. Duplicate bands appeared in control male (lane 1) at approximately 97 KD, but one band completely disappeared in treated samples (lanes 2 to 5). Also the color intensity of this band was reduced in lanes 3 and 5 in males. The present result exhibits changes in the electrophoretic pattern of male mice treated with brodifacoum. The changes may be due to the dose levels or time elapses after treatment. The changes in the electrophoretic distribution of female mice plasma proteins were less noticeable. Similar electrophoretic findings were reported by Colvin and Wang (1974) and Shimaila (1989).

The present study will help in establishing a laboratory method to evaluate the efficacy of the different anticoagulants. The prothrombin time (PT) and partial thromboplastin time (PTT) may be used as a rapid and accurate method for determining the level of resistance to any anticoagulant rodenticides and the susceptibility of the different rodent species to these chemicals. Moreover, measurement of PT and PTT is a satisfactory method for monitoring patients on anticoagulant therapy, as well as poisoning.

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الدراسات التوكسيكولوجيه لمبيدات القوارض المضاده للتجلـــــط (البروديفاكوم والديفنيكوم) على فئران الالبينـــــو

تم دراسة تأثير مبيدى البروديفاكوم والديفانيكوم على بعض الاهداف البيوكيميائيـه ومكونات الدم فى ذكور وأناث فئران الالبينو بعد ٢٤ و ٧٢ ساعه من المعامله . وقد أظهرت النتائج انخفاض عدد خلايا الدم الحمراء وقيم الهيماتوكريت ومحتوى الهيموجلوبين فى الافراد المعامله عن الكنترول ويزداد هذا التأثير بزيادة الجرعه ، بينما يـــزداد عدد خلايا الدم البيضاء . وفى نفس الوقت وجد أن زمن البروثرومبين والثرومبوبلاستين الجزيئى قد زاد بزيادة الجرعه وقد وصل أعلى قيمه له بعد ٧٢ ساعه من المعامله .

وبالنسبه لبعض النظم الانزيميه فقد وجد زيادة نشاط انزيمات الانيلين هيدروكسيليز والادينوسين ثلاث فوسفاتيز والفوسفاتيز الحامض فى كبد الفئران المعامله بينما نشاط انزيم الجلوتامات أو كسالواستيات ترانس امينيز فلم يتأثر بهذه المبيدات . فى حين أنخفـــض نشاط انزيم الفوسفاتيز الحامض فى كلية الفئران المعامله .

ويمكن الاستفاده من هذا البحث فى مكافحة الفئران وفى حماية حيوانات المزرعـــه والعمال المشتغلين بهذه المبيدات .

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