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ACUTE AND SUBCHRONIC TOXICITY OF METHOMYL TO MALE ALBINO RATS

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ABSTRACT

The effect of long-term administration of methomyl on clinical symptoms some organs weight gain, enzymes activities and chromosomal aberration was studied male of albino rats male albino rats (*Rattus norvegicus*) treated with methomyl soluble powder (90%swp) during the experimental period (90 days) by different concentrations (5,10 and 20ppm) that dissolved in drinking water and also the effect of recovery period (30 days) were studied methomyl induce clinical symptoms of toxicity in the different concentrations included lacrimation, convulsion ,hypertension was increased with higher concentrations, where as 5 ppm produced slight symptoms. The organs weight ratio of treated albino rats with 5, 10 and 15 ppm were increased respectively.

On the other hand, in treated rats by different concentrations of methomyl data cleared that the urea and creatinine levels in the treated rats during the experimental period The maximum increase observed in the case of kidney function after exposure to 20 ppm with methomyl. In contrary, a slightly inhibition which correlated with the concentration 5 ppm was observed in the cholinesterase activity (BChE) in plasma of rats.

. The highest chromosomal aberration was observed in treated rats with 1/20 and 1/10 of LD50 doses after 12 and 18 hrs, while the lowest chromosomal aberration was noticed after different intervals in treated rats for 1/40 LD_{50} methomyl.

Keywords: Methomyl, SWP, urea, creatinine, kidney function, ChE and chromosomal aberration.

INTRODUCTION

Although carbamate insecticides are relatively less pharmacologically toxic as anticholinesterase agents in contrast to organophosphorus compounds, The chemical structure, metabolism and distribution on of carbamates as well as its insecticidal activity were extensively studied (Chin *et al.*, 1980 and Osman *et al.*, 1983).

Knowledge about various mechanisms of pesticide interaction should be utilized in predicting the human hazards of pesticides. Consequently, studies on laboratory animals have become the main source of toxicological data. A toxicant may induce several types injury and the severity of effects is usually related to the dose and duration of exposure for assessment of the safety / risk of the chemical under a specified exposure (Frank and Sielkenzr, 1991).

The extrapolation is done by the identification of a no-observed adverse effect level (NOAEl) and the application of a safety factor, there by arriving at an acceptable daily intake (ADI). On the other hand, the (ADI)

approach, which is used before non carcinogenic chemicals and certain non-genotoxic, carcinogensis is intended to estimate a dose that is considered safe in light of the available.

Pesticides are chemicals commonly used to control and eradicate disease vectors, improve agricultural production and protect stored agricultural products. Greater reliance on the use of pesticides to maintain higher agricultural productivity appears inevitable as the demand for food increases with the increase population. In developing countries, the use of pesticides has become so important that their use is inextricably linked with improvement of human welfare (Osibanjo, 1989).

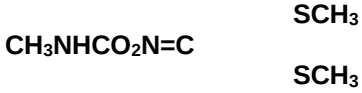
Pesticides are usually applied in their formulated form where the active ingredient is combined with organic solvents, emulsifying and wetting agents which affect the pesticides., The additives may synergize or antagonize the toxicity of the active ingredient (El-Sebae, 1985).

Pesticides are essential for agricultural crops in Egypt as well as in other countries in the world on other hand accidental toxicity from pesticides may occur to the workers during the application to the animals present in the fields during applications.

Toxicity may be established by feeding on contaminated vegetables or others crops leading to variable degree of toxicity. Therefore, the study was initiated to evaluate the effect of Methomyl on the chromosomal aberrations and to investigate the side effect of methomyl on organ weight ratio, cholinesterase activity and kidney function in male albino rats (*Rattus Norvegicus*).

MATERIALS AND METHODS

Chemicals: Insecticide used was the Methomyl (Kuik). The formulation used was soluble powder (90% SWP) containing 90%active ingredient Methomyl (S-methyl N-(methylcarbamoyloxy) thioacetimidate).



Test Animal:

A total of 60 male albino rats weighing 120 ± 10 gm were selected for the present experiment. Rats were housed in cages for groups of six in air conditioned room and were provided with 23% protein diet and water *ad lebitum* through the experimental period.

Determination of Medium Lethal dose LD_{50}:

The medium lethal dose LD_{50} was determined according to Weil (1952), owing to its simplicity and few numbers of experimental animals required, This method also reduces the time of calculations of the LD_{50} and its confidence intervals to the minimum without the sacrifice of accuracy.

In this method a group of tables had been calculated and designed to allow the use of 2,3,4,5,6 or 10 animals per dosage level, with 4 or more dosage levels being tested per material.

The steps that followed to use such method are:
(a)Four animals were dosed on each dosage level group.
(b)The constant ratio between dosage level was 1.26.
(c)Animals were dosed 4 successive dosage levels.

When the mortality data (r-values) were obtained, we seek to obtain the f-values from the tables. The LD_{50} can be calculated from the following formulas:

Log m = Log D + d (f+1)

Anti log m = LD_{50}

Forty male of albino rats were separated into four groups of ten rats each and treated as follow:

- Group (A) rats were kept as control (untreated) for comparison.

Group (B), (C) and (D) rats were treated with methomyl through drinking water at concentrations of 5, 10 and 20 ppm respectively for 90 days. The groups of treated animals were left for 30 days (recovery period) after with drawel the tested insecticide.

The blood samples were drawn by orbital sinus technique into a containers with heparin as anticoagulant (10 IU ml blood) At intervals of 15, 30, 45, 60, 90 and 120 days, (Schalm, 1986). For determination urea and creatinine was carried out by using commercial reagent kits according to the method of Coulombe and Farreau (1963), Husdan and Rapapret (1968). Cholinesterase (BChE) activity was according to the method of Den Blawen *et al.* (1983). At the end of treatment (90 days), five animals from each group were killed and interval organs (liver, kidney, spleen, heart, lung and brain) were quickly removed and weighed.

To determine chromosomal aberrations in bone marrow cells, each experimental group was consisted of 5 treated and 5 untreated males. Rats were treated intraperitoneal (I.P). The bone marrow was sampled from the femur at 6, 12, 18 and 24 hrs after treatment with sublethal doses 1/10, 1/20 and 1/40 LD_{50} of methomyl for adult albino rats obtained (Frank and Sielkenjr, 1991). The rats were injected with 0.1 ml of a colchicine solution corresponding to a dose of 2 mg/kg.

Two hr before sampling. Air-dried bone marrow slides were stained with 2% acetic orcien. For each group 1000 mitoses were analyzed. The preparation and scoring procedure has been described by Alder and El-Tarras (1989). Chromosomal aberrations were scored under 100 x phase contrast. Mitotic indices were determined by counting the number of dividing cells among 1000 cells per animal in the bone marrow cells.

RESULTS AND DISCUSSION

Methomyl acute oral LD50 value and confidence limits for adult rats are presented in Table (1) .The results agreement with (Meehan, 1984). This may be due to high activity of growing animals through this period of development, this finding is expected it is well known that pesticides are more toxic in adult. The toxic observation obtained from rats received different concentrations of methomyl in drinking water (5,10 and 20 ppm) for (90 days) and recovery period in subchronic study.

Table (2) shows that the clinical signs of methomyl included lacarimation convulsion hpertension, hypoactivity and muscular weakness were manifested in determination different concentrations (5,10 and 20 ppm) methomyl similar results were observed by Harbison (1974) found that adult rats were more sensitive to methomyl and recorded an altered behavior obvious in highly Concentrations 20 ppm more than (5 and 10 ppm) of methomyl.

Data in Table (3) show weight gain ratio of liver, kidney, spleen, heart, lung, brain and supra renal gland, while treatment of 5 and 10 ppm methomyl showed no differences in organ weight gain ratios of liver, kidney, spleen, heart, lung, brain and supra renal gland. From these results it could be seen that through the tested doses (5,10 and 20 ppm) only the highest dose revealed an increase in organ weight gain of rats as compared to control. These results are in agreement with those obtained by Cannon and Kimbrough (1979), who reported that, treatment of rats by low doses of chlordecone showed no differences in organs weight, except the liver Also results are in agreement with those of Hassan *et al.* (1989), who found that organ weight gains were increased in rats treated with high dose of methomyl and no changes were observed in low dose.

They added that an increase in liver weight may be attributed primarily to hepatocytoma, increase in endoplasmic and excen lipid accumulation a result to chronic effect of dimethoate and deltmethrin on rabbit.

Table (4) clear that methomyl caused elevation in urea concentration at 5, 10 and 20 ppm respectively during the 90 days of treatment On the other hand, there was recovery periods (30 days) in urea concentration 5, 10 and 20 ppm respectively after 90 days of treatment Our results are in agreement with Hassan *et al*. (1989). Who concluded that carbamate insecticides increased urea in different doses in rats. This increase in plasma could be attributed to the changes in creatinie. Similar results were observed by Ameno *et al.* (1994).

Concerning, the creatinine level, Data revealed that, the methomyl led to increase in creatinine level after 15 and 60 day from treatment at the low and high doses urea nitrogen levels serve as a rough predictine index of symptomatic renal failure and as diagnostic aid in distinguishing among the various causes of renal insufficiency (Anderson and Cockoyne, 1989).

It is appear that, the methomyl doses in drinking water caused elevation in urea concentration and creatinine level.

These parameters (urea and creatinine) are used as an index of renal damage in living organisms (Coles, 1986). The obtained results are in agreement with those reported by Srivastava and Rampal (1989). Hanafy *et al.* (1991) and Asghar *et al.* (1995) who mentioned that the urea and creatinine levels elevated significantly in treated animals (calves, rats and rabbits) after treatment with some organophosphorus insecticides (Quinalphos, Methomidophos and Methyl parathion). In contrary Naser *et al*. (1996) mentioned that, treatment rats with phoxim revealed no changes in creatinine.

Table (1): Acute toxicity of oral (PO) methomyl to male adult albino rats.

Insecticides	LD_{50} mg/kg (PO) Adult
Methomyl	19.63 Confidence limits among (15.49 – 24.49)

Table (2): Toxic symptoms in male adult albino rats administered formulated methomyl for three months.

Treatment	Signs of Toxicity	Mortality of Animals
	Adult	Adult
Control	Nil	Nil
5 ppm	Lacrimation	Nil
10 ppm	Convulsion and hypertension	Nil
20 ppm	Hypoacativity and muscular weakness	Nil

Table (3): Effect of prolonged oral administration of methomyl to male albino rats for 90 successive days on internal organs weights ratio (gm/100 gm b.wt.).

Concentration Parameters	Control	5 ppm	10 ppm	20 ppm
Liver	10.22±0.1	9.80±0.07*	9.32±0.19*	10.96±0.29
Kidney	4.44±0.06	4.56±0.06	4.37±0.06	4.61±0.17
Spleen	2.56±0.15	2.67±0.08	2.80±0.10	3.13±0.06*
Heart	3.24±0.16	3.39±0.02	3.33±0.12	3.28±0.09
Lung	4.13±0.06	4.13±0.23	4.22±0.14	4.15±0.07
Brain	4.59±0.08	4.43±0.10	4.02±0.19	4.27±0.08
Supra renal gland	0.86±0.14	1.017±0.19	0.97±0.25	0.63±0.06

Mean ± S.E.*
Mean significantly different from the control (P< 0.05).

Our results are also in accordance with Nariman *et al.* (1999), who reported that the repeated exposure of rats to Thiodicarb led to elevation the urea in blood.

Table (5) represents the butyril cholinesterase (BChE) activity of adult male rats exposed to different concentrations of methomyl a slightly inhibition could be observed in the activity of (BChE) in plasma for the low concentration 5 ppm. Methomyl caused significant changes in the activity of plasma (BChE) after treatment with the higher concentrations 10 and 20 ppm respectively. The activity of plasma (BChE) showed different effect either in high or low doses at the experimental period.

In this respect, Claudie *et al.* (1979) found that carbamate insecticides or their active metabolites apparently reach several tissue very quickly after administration through oral route.

Results emphasized that (BChE) activity of treated rats have returned to the normal range as in control treated rats. It could be stated that the hydrolysis of carbamylated cholinesterase is more rapid than the phosphorylated enzyme (O'Brien 1967, Westlake *et al.*1981 and Hassal 1987).

Data in Table (6) presents the results of aberration analysis in mitotic chromosomes of bone marrow cells. The highest chromosomal aberrations of methomyl was occurred by 1.9 and 0.95 mg/kg at 12 and 18 hrs after treatment respectively. Methomyl. The lowest chromosomal aberrations occurred at the level of 0.47 mg/kg of the methomyl at the two previously mentioned intervals. No cytotoxic effect at 6 or 24 hrs after treatment with all doses occurred. The reduction of mitotoxic index was compared to the solvent treated rats as control.

The aberrations seen were of the chromatid type i.e. gaps, breaks and no exchanges. Illustrated in Figs (1,2 and 3). The doubling dose is the dose, which induces as many aberrations as occur spontaneously per cell cycle. It can be calculated on the basis of a linear dose-response relationship as the quotient of the spontaneous frequency and the regression coefficient, best fits a linear quadratic equation. The doubling dose at 12 hrs in the dose response Y = 1.2 +44D and the doubling dose at 18 hrs Y = 1.2 + 49 D to compare the different doses in the methomyl from the chromosomal aberrations.

Rupa *et al.* (1991) observed that a high frequency of sister chromatid exchange (SCE) was observed in males occupationally exposed to different pesticides for different time intervals.

The rate of (SCE) in males treated with organochlorine, organophosphorus and carbamate pesticides may cause damage to somatic cells and low mitotic index in agricultural workers even in the absence of smoking or alcohol consumption.

Carbamates insecticides were previously recorded to be positive in short-term mutagenicity assay. These compounds increased the formation of chromosomal aberrations, micronuclei in mice and human lymphocytes DNA single strand breaks and mitotic abnormalities. Furthermore they are able to induce such aberrations in both animals and plant cells. (Fahrig and Seiler, 1979 and Zelesco *et al.*1990).

Similar results were observed by Soheir *et al.* (1995). Found that carbamate in higher dose are effective in inducing chromosomal abnormalities than lower doses. These determinations may explore and help in establishing the no observed adverse effect level (NOAEL) lowest concentration.

The present study has shown that low concentration of methomyl 5ppm could be considered near to that of no observed adverse effect level (NOAEL). Identification of no-observed adverse effect level (NOAEL) and the application of a safety factor would thereby, assist in arriving at an acceptance. It is highly indicated to protect animals from accidental ingestion and oral of high concentrations of methomyl or long-term exposure to it.

Fig (1): Rat bone marrow, normal metaphase (X 2000).
Fig (2): Rat bone marrow metaphase showing Chromatid gap (g) (X 2000).
Fig (3): Rat bone marrow metophase showing chromatid break (Br) and fragment (F) (X 1000).

Table (6): Frequencies of aberrations in affected bone marrow cells of adult male albino rat after treatment with methomyl subchronic doses.

Dose mg/kg	Interval (h)	Number of Cells	Gaps (n)	Breaks	Fragment	Exchange	M.I.
Control	6, 12, 18, 24	800	3	5	0	0	5.1
1.9	6	500	11	7	3	0	3.9a
	12	500	21	8	2	0	3.8b
	18	500	22	5	4	0	3.8b
	24	500	15	3	0	0	4.2b
0.95	6	500	12	5	1	0	4.2b
	12	500	20	8	2	0	4.1a
	18	500	22	4	5	0	4.0b
	24	500	14	2	6	0	4.7b
0.475	6	500	7	4	1	0	4.6a
	12	500	16	7	1	0	3.8b
	18	500	13	9	3	0	3.6b
	24	500	10	4	3	0	4.5b

a) Non significant P < 0.01, P < 0.05
b) Significant P < 0.01, P < 0.05

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السميه الحادة وتحت المزمنه لمبيد المثيوميل لذكور فئران التجارب

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المعمل المركزى للمبيدات قسم سميه الثدييات قسم الحشرات الاقتصاديه والمبيدات – كليه الزراعه جامعه القاهرة

يهدف البحث الى دراسه السميه الحادة وتحت مزمنه لمبيد المثيوميل لذكور فئران التجارب باستخدام ثلاث تركيزات للمركب المختبر وهى 5 ،10 ،20 جزء فى المليون لمدة ثلاث شهور من المعامله فى ماء الشرب وفتره شهر للاسترجاع 0

أظهرت النتائج ان التركيزات الاعلى 20 جزء فى المليون من المركب له تأثير واضح على أعراض التسمم المختلفه وعلى وزن الأعضاء المختلفة والنشاط الانزيمى لوظائف الكلية يوريا وكريانتين وكذلك على نشاط انزيم الكولين الاستريز بسيرم الدم 0

أوضحت النتائج أن مستوى الجرعه العاليه له تأثير واضح على معدلات التغيرات الكروموسوميه الجسميه 10/1 ،20/1 من الجرعه السامه النصفيه وانخفضت بوضوح بمستوى الجرعه المنخفضه 40/1 من الجرعه السامه النصفيه للمركب المختبر 0

Table (4): Effect of prolonged oral administration of methomyl to male albino rats for 90 successive days on kidney function.

Periods		15 days				30 days			
Conc. / Parameters	Pre-treatment	Control	5 ppm	10 ppm	20 ppm	Control	5 ppm	10 ppm	20 ppm
Urea (g/L)	0.688±0.04	0.466± 0.03	0.489± 0.05	0.433±0.02	0.598±0.05	0.559±0.02	0.927±0.01***	0.664±0.08	0.704±0.10
Creatinine (mg/dL)	0.391±0.06	0.368± 0.09	1.242±0.24*	1.084±0.31	0.542±0.03	0.484±0.06	0.368±0.08	0.207±0.04*	0.276±0.10
Periods	**Pre-treatment**	**45 days**				**60 days**			
Conc. Parameters		**Control**	**5 ppm**	**10 ppm**	**20 ppm**	**Control**	**5 ppm**	**10 ppm**	**20 ppm**
Urea (g/L)	0.688±0.04	0.663±0.04	0.507±0.03	0.551±0.02	0.539±0.030	0.569±0.03	0.500±0.055	0.541±0.01	0.696±0.06
Creatinine (mg/dL)	0.391± 0.06	0.461±0.12	0.230±0.05	0.281±0.03	0.364±0.024	0.124±0.01	0.228±0.044	0.352±0.09	0.419±0.02 ***
Periods	**Pre-treatment**	**90 days**				**Recovery Periods (30 days)**			
Conc. Parameters		**Control**	**5 ppm**	**10 ppm**	**20 ppm**	**Control**	**5 ppm**	**10 ppm**	**20 ppm**
Urea (g/L)	0.688± 0.04	0.609±0.020	0.768±0.04*	0.478±0.01	0.464±0.01**	0.905±0.07	0.940±0.08	0.746±0.10	0.999±0.07
Creatinine (mg/dL)	0.391±0.06	0.285±0.02	0.270±0.03	0.328±0.03	0.371±0.04	0.600±0.07	0.500±0.07	0.450±0.12	0.675±0.11

Mean ± S.E. *****

Mean significantly different from control (P < 0.05)

**** Mean significantly different from control (P < 0.001)** *******

Mean significantly different from control (P < 0.0001)

Table (5): Effect of prolonged oral administration of methomyl to male albino rats for 90 successive days on butyril cholinesterase (B-ChE).

Period Conc. / Parameters	Pre-treatment	15 days				30 days			
		Control	5 ppm	10 ppm	20 ppm	Control	5 ppm	10 ppm	20 ppm
		158.6±10.64	143.6±15.17	173.4±18.4	156.8±9.96	169.2±15.51	178.0±7.3	169.0±16.29	193.2±20.5
		45 days				60 days			
		Control	5 ppm	10 ppm	20 ppm	Control	5 ppm	10 ppm	20 ppm
Serum B-ChE (U/L)	182.2±14.26	163.0±16.86	160.0±26.3	164.2±41.1	138.0±11.8	185.8±11.8	166.01±12.4	136.9±10.1	222.0±38.0
		90 days				Recovery Periods (30 days)			
		Control	5 ppm	10 ppm	20 ppm	Control	5 ppm	10 ppm	20 ppm
		157.0±12.5	164.4±15.0	195.6±36.9	131.2±25.5	134.2±16.0	188.8±16.3	164.0±12.3	117.8±11.2

Mean ± S.E.

*** Mean significantly different from the control (P < 0.05)**