HAEMATOLOGICAL, BIOCHEMICAL AND HISTOPATHOLOGICAL ALTERATIONS INDUCED BY ABAMECTIN AND *Bacillus thuringiensis* IN MALE ALBINO RATS

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ABSTRACT

The renal and hepato-toxicity induced by abamectin pesticide (Vertimec) and a commercial formulation of a bio-insecticide *Bacillus thuringiensis* (Agerin) in male albino were evaluated. Blood picture and blood glucose level were investigated as well. Male albino rats were administered daily dietary doses each equivalent to 1/10 or 1/100 of the LD_{50} values of each toxicant. Treatments continued for 30 consecutive days. Abamectin was found to pose risks of renal and hepato-toxicity in rats. Since biochemical parameters of liver function (i.e. aspartate aminotransferase activity, alanine aminotransferase activity, acid phosphatase activity, albumin, and total protein levels) and kidney function (uric acid and creatinine concentration) were severely affected. These effects were ensured by histopathological examination of liver and kidney tissues. Likewise, some haematological indices (i.e. erythrocyte count, leukocyte count and haemoglobin concentration) were also influenced, in addition abamectin might be hypoglycemic. On the other hand, the above mentioned lesions were relatively obscure in the case of *Bacillus thuringiensis*-treated rats.

Key words: abamectin, *Bacillus thuringiensis*, rats, blood picture, liver parameters, kidney indices, histopathology.

INTRODUCTION

Increased public concern of the potential adverse environmental effects associated with the heavy use of chemical pesticides has prompted the examination of alternative methods for pest control. Two of the promising alternatives are the use of abamectin which is a natural product pesticide isolated from the fermentation of the soil actinomycete, *Streptomyces avermitlis* and the microbial insecticide *Bacillus thuringiensis* (Bt). Abamectin

which has potent anthelmintic, acaricidal and insecticidal properties (**Wehner *et al.*, 1993** and **Shoop *et al.*, 1995**),acts by stimulating the pre-synaptic release of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), binding to the post-synaptic receptors (i.e. GABA agonist) and thus disturbing Cl^- passage through the end plate resulting in the inhibitory post-synaptic potentials and eventual paralysis (**Husten and Roberts, 1985** and **Corbitt *et al.*, 1992**). Bt has a high efficacy against certain species of insects of the orders, Lepidoptera, Diptera, Homoptera and recently Coleoptera (**El-Hamady, 1997-a**). Bt produces a parasporal inclusion body during sporulation usually referred to as a crystal. This crystal is made of proteins and exert its mode of action by dissolving in the alkaline environment of the host insect midgut causing lysis of the midgut epithelial cells membranes, eventually leading to death of the larvae (**Höfte and Whitely, 1989;Gill *et al.*,1992; Bauer, 1995 and Joung and Cote,2000**) Therefore, the main target of the present study is to investigate their side effects on some haematological, hepatic and renal parameters as well as histopathological changes in white albino rats.

MATERIALS AND METHODS

Pesticides used:

- **Vertimec (Abamectin) 1.8% E.C.:** a mixture containing a minimum of 80% avermectin B_1a (5-0-demethylavermectin A_1a) and a maximum of 20% avermectin B_1b (5-0-demethyl-25-de-(1-methylpropyl)-25-(1-methylethyl) avermectin A_1a). Producing company: MSD AGVET; MSD sharp & Dohme GmbH, Germany
- **Agerin *(Bacillus thuringiensis)* 6.5% W.P.:** Producing company: Biogro International-Egypt.

Test animals:

Adult male albino rats (Sprague-Dawely), *Rattus norvegicus albinus*, weighting 110-120 gm were purchased from the Biological Products & Vaccines Holding Company, Helwan Farm, Cairo. Rats were kept under the laboratory conditions of 25 ± 5°C and 65 ± 5% R.H., two weeks as an acclimatization period. They were housed in metal cages (35 x 25 x 20 cm) and maintained on *ad libitum* diet and water. This diet contained all the dietary

needs and was obtained from Alexandria Oil and Soap Company, Ghamra, Cairo.

Assessment of the oral LD_{50} for the tested pesticides:

Preliminary investigation was carried out to calculate the median lethal dose (LD_{50}) for the tested pesticides to male albino rats. Four groups of rats, each of three individuals (n = 3) were used for each toxicant. Rats of each group were given orally the specified dose for each toxicant. Doses were prepared in corn oil. Oral dosing was done by a special syringe that has a needle equipped with a ball tip. Mortality counts of rats were recorded after 24 hours of treatment. The LD_{50} values were calculated according to the statistical method of **Weill (1952)**. Results demonstrated that, the oral LD_{50} values of Vertimec and Agerin to male albino rats are 18.1 and >3000 mg a.i./kg b.w., consecutively.

Experimental design:

Rats were divided randomly to five groups, each of five rats. The first and second groups received diet containing abamectin at quantities equivalent to 1/10 and 1/100 of the LD_{50} values, respectively. The third and fourth groups received diet containing *Bacillus thuringiensis* at quantities equivalent to 1/10 and 1/100 of the LD_{50} values, respectively. The fifth group received pesticide-free diet and was considered as a control. Feeding administration lasted for thirty successive days. At the end of this period, rats were weighed, slaughtered and blood samples were immediately collected. Livers and kidneys of rats were dissected out, trimmed of excess fat and weighed. Therefore, hematological, biochemical and histo-pathological studies could be carried out.

Preparing of the toxicated diet:

To calculate the quantities of pesticides required to be mixed with diet, exploratory experiments were performed to determine the quantity of the diet normally consumed by each rat per day. Five male rats were caged individually, starved and each was offered adequate weighed quantity of diet. After 24 hr, the residual quantity of diet was thoroughly collected and weighed. Average weight of diet consumed daily by each rat was calculated. Determination of individual feed consumption was determined periodically according to ages and body weights of the tested animals during the experimental period. The desired quantity of each pesticide was diluted in a proper volume of water and mixed

thoroughly with diet. The mixture was allowed to dry at room temperature and then kept in a deep freezer till being used. This mixture was considered a fresh treated diet for three days, afterwards, new mixtures were periodically prepared by the same manner. The ratio of pesticide/diet in the mixture was calculated on the basis that toxicated diet ingested by an animal/24 hr, should carry the required quantity of a pesticide that is nearly equivalent to the desired dose calculated as fraction of LD_{50} of this pesticide. Variations of body weights of animals through the experimental period were taken in consideration. Freshly prepared toxicated diet and clean water were offered daily to rats *ad-libitum*, for 30 consecutive days.

Blood samples:

At the end of this experiment (30 days), blood samples were individually collected from each rat, immediately after slaughtering in dry clean centrifuge tubes and divided into two portions. The first portion was taken on heparin as anticoagulant (1-2 IU/ml) for haematological examination. The second portion was left to clot at room temperature for about 20 min. and then centrifuged at 3000 r.p.m for 15 minutes, the supernated serum samples were drown in dry clean-capped tubes and kept in deep freezer at -20°C until conducting the biochemical analysis.

Haematological examination:

Red blood cells (RBCs) and white blood cells (WBCs) were counted as described by **Dacie and Lewis (1984)**, while haemoglobin concentration (Hb) was measured according to **Vankampen and Zijlstra (1961)**.

Biochemical analysis:

Activities of some enzymes and concentrations of certain biochemical parameters representing liver and kidney functions were determined in the rats blood sera colorimetrically as follows: Aspartate and alanine aminotransferase (AST & ALT) activities were determined according to the method of **Schmidt and Schmidt (1963)**, whereas acid and alkaline phosphatases (ACP & ALP) activities were determined as described by the method of **Young (2001)** and **Belfield and Goldberg (1971)**, successively. Total protein, albumin, glucose, cholesterol, uric acid and creatinine concentrations were determined according to the methods of **Domas (1975)**, **Drupt (1974)**, **Tietz (1986)**, **Schettler**

and Nussel (1975), Duncan (1982) and **Henry (1974)**, respectively . All determinations were done by using U.S.A. Spectrophotometer Spekol 11.

Histopathological study:

The influence of the tested pesticides on the histopathology of liver (the essential organ for drug metabolism) and kidney (the essential organ for drug excretion) was investigated. At the end of this experiment (30 days), liver and kidney from each sacrificed rats were dissected out, trimmed of excess fat and weighed (the relative weight of the organ equals the weight of the organ divided by the weight of whole rat body). Then, the liver and kidney were fixed in 10% neutral formalin and prepared for histopathological examination according to **Lilie and Fullmen (1976).**

Statistical analysis:

Statistical analysis of toxicological experiment data was carried out according to Duncan multiple range test (**Duncan, 1955**).

RESULTS AND DISCUSSION

1- Effect on haematological parameters:

Data recorded in Table (1) reveal that Vertimec caused reduction in erythrocyte counts (RBCs), leukocyte counts (WBCs) and haemoglobin concentration. These effects were significantly more pronounced in Vertimec- treated rats at the high dose.The reduction in erythrocyte counts and consequently haemoglobin conc. may be attributed to more than one factor, i.e. the failure to supply the blood circulation with cells from haemohepatic tissues, since the liver has an important role in the regeneration of erythrocyte, and the possible destructive effect on erythrocyte by the toxicants (**Abdel-Mouty, 1996**). The obtained results are in agreement with those found by **Ali, (1990) and Anubama *et al.*, (2001)** who stated that avermectins reduced erythrocyte, leukocyte counts and haemoglobin concentration in rabbits and rats. On the other hand, no haematological changes were found in the treated rats with Agerin by far. Similar results for *Bacillus thuringiensis* were observed by **Tsai *et al.*, (1996)**.

Table (1): Counts of red, white blood cells and haemoglobin concentration in blood of male albino rats fed on contaminated rations with tested toxicants for thirty successive days.

Treatment	RBCs ($\times 10^6$ / µl)		WBCs ($\times 10^3$ / µl)		Haemoglobin (gm %)	
	count	% of control	count	% of control	Conc.	% of control
1/10LD_{50} Vertimec	3.31^{c}	77.52	2.97^{b}	74.62	14.229^{b}	90.91
1/100 LD_{50} Vertimec	3.83^{b}	89.69	3.72^{a}	93.47	15.039^{ab}	96.08
1/10LD_{50} Agerin	3.88^{b}	90.87	3.80^{a}	95.48	15.665^{a}	100.08
1/100 LD_{50} Agerin	3.95^{ab}	92.51	3.98^{a}	100.00	15.849^{a}	101.25
Control	4.27^{a}	100.00	3.98^{a}	100.00	15.652^{a}	100.0

- Values across each column having the same superscript letter (s) were not significantly different ($p < 0.05$).

2- Effect on liver function parameters:

Liver is often the primary target for the toxic effects of xenobiotics. It is known that the detoxification of the toxic materials which enter the body occurs mainly in the liver **(Balisteri and Shaw, 1987)**. Therefore, liver can be used as an index for the toxicity of xenobiotics. Hence, the activities of some enzymes and levels of certain biochemical parameters representing liver function, i.e. AST, ALT, ACP, ALP, total protein, albumin, and cholesterol were determined in treated and untreated rats. Data in Tables (2 and 3) illustrate that Vertimec elevated the activity of AST and acid phosphatase (ACP) and decreased ALT activity, total protein, albumin, and glucose concentrations in serum of treated rats in a dose-dependent manner, whereas alkaline phosphatase (ALP) activity and cholesterol concentration remained unaltered. On the contrary, Agerin at both dose levels was innocuous for most chosen liver function indices with the except of elevation of ACP activity and reduction of total protein concentration just at its high dose. The aforementioned findings are in coincidence with those reported by **Eweis *et al.*, (1995)** who observed a decrease in ALT activity and total protein concentration in treated rats with ivermectin at 1/10 LD_{50} level.; **El-Hamady (1997-b)** who found that Vertimec increased AST activity and decreased total protein concentration in rats serum; and **Halkova *et al.*, (1993)** who stated that *Bacillus thuringiensis* revealed no significant changes in biochemical parameters of sexually mature Wistar rats. Aminotransferases play an important role in amino acids metabolism and biosynthesis. Consequently, they are considered as specific indicators of liver damage **(Uppal and Ahmed 1977)**.

Table (2): Serum aminotransferases and phosphatases activities of male albino rats fed on contaminated rations with tested toxicants for thirty successive days.

Treatment	AST (U/L)		ALT (U/L)		Acid phosphatase (U/L)		Alk. phosphatase (IU/L)	
	activity	% of control	activity	% of control	activity	% of control	activity	% of control
1/10LD$_{50}$ Vertimec	67.65^{a}	194.23	15.95^{b}	68.16	17.25^{a}	170.37	211.77^{a}	100.78
1/100 LD$_{50}$ Vertimec	60.02^{a}	172.32	20.63^{a}	88.16	14.25^{ab}	140.74	207.97^{a}	98.97
1/10LD$_{50}$ Agerin	35.94^{b}	103.19	22.36^{a}	95.55	16.13^{a}	159.26	209.96^{a}	99.91
1/100 LD$_{50}$ Agerin	34.93^{b}	100.29	23.57^{a}	100.73	13.88^{ab}	137.04	209.78^{a}	99.83
Control	34.83^{b}	100.00	23.40^{a}	100.00	10.13^{b}	100.00	210.14^{a}	100.00

-Values across each column having the same superscript letter (s) were not significantly different ($p< 0.05$).

Table (3): Concentration of total protein, albumin, cholesterol and glucose in serum of male albino rats fed on contaminated rations with tested toxicants for thirty successive days.

Treatment	Total protein (gm%)		Albumin (gm %)		Cholesterol (mg %)		Glucose (mg %)	
	level	% of control	level	% of control	level	% of control	level	% of control
1/10LD$_{50}$ Vertimec	7.60^{b}	86.27	5.63^{b}	84.16	34.17^{a}	98.19	60.79^{c}	82.71
1/100 LD$_{50}$ Vertimec	8.09^{b}	91.83	6.68^{a}	99.85	34.80^{a}	100.00	65.38^{bc}	88.95
1/10LD$_{50}$ Agerin	7.61^{b}	86.38	6.63^{a}	99.10	33.12^{a}	95.17	66.13^{abc}	89.97
1/100 LD$_{50}$ Agerin	8.63^{a}	97.96	6.66^{a}	99.55	33.75^{a}	96.98	70.09^{ab}	95.36
Control	8.81^{a}	100.00	6.69^{a}	100.00	34.80^{a}	100.00	73.50^{a}	100.00

- Values across each column having the same superscript letter (s) were not significantly different ($p< 0.05$).

The alteration in serum levels of aminotransferases (AST & ALT) may be indicative of internal organs damages specially in liver (**Kaneko *et al.*, 1997**). The elevated acid phosphatase activity may be associated with the cell disintegration resulting from pesticide treatment, thus suggesting prenecrotic changes in the liver tissues (**Saigal *et al.*, 1982**). Qualitative and quantitative disturbance of protein synthesis is a consequence of impaired hepatic function (**Celia and Wilkinson, 1973**). Hypoalbuminemia (decreased albumin) is a liver disorder thought to be a consequence of decreased hepatic synthesis of albumin (**Burtis and Edward, 1994**).

3- Effect on kidney function parameters:

Results in Table (4) show that Vertimec increased uric acid and creatinine concentrations in serum of treated rats in a dose-dependent manner. On the other hand, Agerin at both dose levels had no adverse effect on uric acid and creatinine concentrations in serum of treated rats. The above findings are in accordance with those reported by **El-Hamady (1997-b)** who found that uric acid and creatinine concentrations were increased in serum of Vertimec-treated rats. Uric acid and creatinine are useful in early deduction of nephrotoxicity induced by exogenous compounds. These parameters are used as index of renal damage in living organisms **(Coles, 1986)**. Elevation of uric acid and creatinine concentration in serum of treated male albino rats may be attributed to reduction in glomerular filtration in the kidney and also reflect dysfunction of the kidney tubules **(Hayes, 1989 and Walmsley and White, 1994)**.

Table (4): Concentration of uric acid and creatinine in serum of male albino rats fed on contaminated rations with tested toxicants for thirty successive days.

Treatment	Uric acid (mg %)		Creatinine (mg %)	
	level	% of control	level	% of control
1/10LD_{50} Vertimec	3.65^{a}	177.18	1.23^{a}	165.54
1/100 LD_{50} Vertimec	2.44^{b}	118.45	1.07^{a}	144.01
1/10LD_{50} Agerin	2.15^{b}	104.37	0.736^{b}	99.06
1/100 LD_{50} Agerin	2.03^{b}	98.54	0.723^{b}	97.31
Control	2.06^{b}	100.00	0.743^{b}	100.00

- Values across each column having the same superscript letter were not significantly different ($p < 0.05$).

4- Histopathological changes:

a. Relative weights of male albino rats organs:

Results in Table (5) indicate that administration of Vertimec and Agerin at both dose levels resulted in a significant increase in the relative weight of treated male rat's liver in comparison with that of control rats. On the other hand, Vertimec and Agerin exhibited no significant alteration in the relative weight of treated male rat's kidney in comparison with that of control rats. Explanation of liver enlargement could be due to the accumulation of abnormal amounts of fat, predominately triglyceride, in the parenchymal cells. Triglyceride accumulation is a result of an imbalance between the rate of synthesis and the rate of release of triglyceride by the parenchymal cells into the systemic circulation **(Plaa, 1975)**.

Table (5): Weights of livers and kidneys of male albino rats fed on contaminated rations with tested toxicants for thirty successive days.

Treatment	Post treatment body weight (gm)	Liver		Kidney	
		weight (gm)	% weight	weight (gm)	% weight
1/10LD_{50} Vertimec	226.66	7.61	3.36[a]	1.63	0.717[a]
1/100 LD_{50} Vertimec	202.70	6.77	3.35[a]	1.42	0.710[a]
1/10LD_{50} Agerin	225.70	7.93	3.55[a]	1.55	0.691[a]
1/100 LD_{50} Agerin	205.00	6.95	3.38[a]	1.34	0.654[a]
Control	205.33	5.80	2.83[b]	1.27	0.624[a]

- Values across each column having the same superscript letter were not significantly different ($p < 0.05$).

b. Liver and kidney histopathological examination:

The normal structure of control male rat's liver and kidney is shown in (Fig. 1 and 4, respectively). Portal tract infiltration by lymphocytes and a focus of dysplasia with cytological atypia were observed in Vertimec-treated male rat's liver at either dose levels (Fig. 2), while Agerin at the high dose solely caused mild portal tract infiltration by lymphocytes (Fig. 3). **El-Banhawy *et al.*, (1993)** found a remarkable abundance of lymphocytes infiltration in the liver tissues post-drug- administration, and postulated that such changes were a prominent response of body tissues facing any injurious impacts. Many reports had elucidated that hepatocellular damage could be correlated with the disturbed enzymes activities. In this respect, **Martin *et al.*, (1983)** announced that liver tissues which were famous for their rich contents of aminotransferases (AST & ALT) suffer markedly from their loss under many pathological conditions. Thus, the biochemical parameters data obtained from this investigation support this speculation in which Vertimec- treated rats showed alteration in the activities of aminotransferases (AST & ALT). Concerning the kidney, Vertimec at either dose levels induced interstitial nephritis in male rat's Kidney (Fig. 5), whereas Agerin caused hyaline globules inside the tubules with thickened membrane denoting nephritis (Fig. 6).

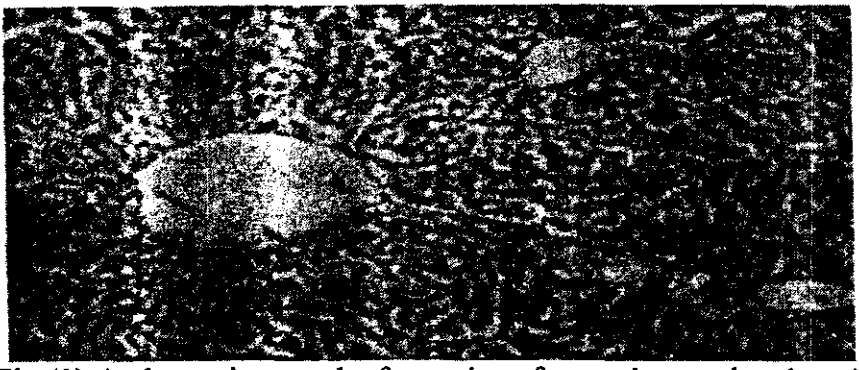

Fig.(1):A photomicrograph of a section of normal control male rat's liver (H & E.x 10).

Fig.(2):A photomicrograph of a section of Vertimec-treated male rat's liver at 1/10 LD_{50} level showing excess portal tract infiltration and a focus of dysplasia with cytological atypia (H & E.x 40).

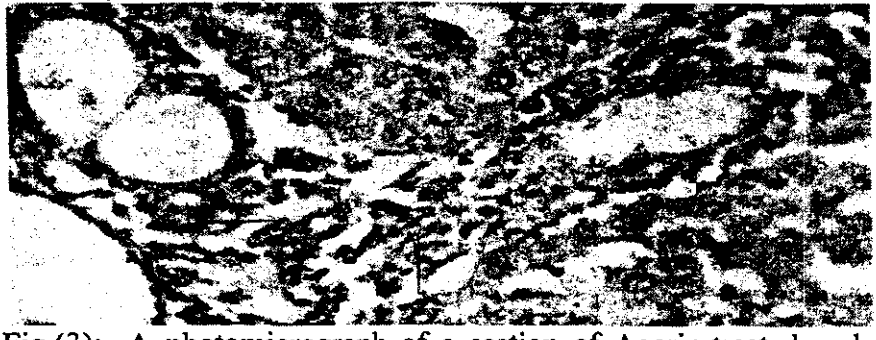

Fig.(3): A photomicrograph of a section of Agerin-treated male rat's liver at 1/10 LD_{50} level showing mild portal tract infiltration by lymphocytes (H & E.x 40).

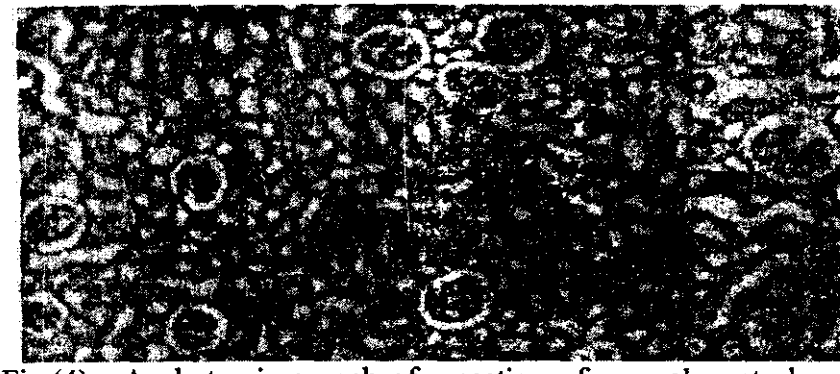

Fig.(4): A photomicrograph of a section of normal control male rat's kidney (H & E.x 10).

Fig.(5): A photomicrograph of a section of Vertimec-treated male rat's kidney at 1/10 LD_{50} level showing interstitial nephritis (H & E.x 40).

Fig.(6): A photomicrograph of a section of Agerin-treated male rat's kidney at 1/10 LD_{50} level showing hyaline globules inside the tubules with thickened membrane denoting nephritis (H & E.x 40).

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التغيرات الهيماتولوجية والبيوكيميائية والهستوباثولوجية فى ذكور الفئران البيضاء الناجمة عن الابامكتين والباسيلس ثيورينجينسيس

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*** قسم البيئة والزراعة الحيوية ــ كلية الزراعة بالقاهرة ــ جامعة الأزهر**

**** قسم المبيدات ــ كلية الزراعة بكفرالشيخ ــ جامعة طنطا**

أجريت هذه الدراسة لتقييم السمية الكبدية والكلويه لمبيد الأبامكتين (فيرتيمك) والتجهيزه التجارية من المبيد الحيوى *Bacillus thuringiensis* (*B. t.*) (أجيرين) وكذلك بحث تأثيرهما على بعض مؤشرات الدم ومستوى الجلكوز فى الدم حيث تم إعطاء ذكور الفئران البيضاء جرعات يوميه عن طريق خلطها بالغذاء كل منها يعادل 1/10 LD_{50} ، 1/100 LD_{50} واستمرت المعاملة لمدة ثلاثون يوما متوالية. وأوضحت النتائج أن مبيد الابامكتين قد أحدث تأثيرات سامة على كبد وكليه الفئران المعاملة وتمثل ذلك فى التأثير عكسيا على نشاط إنزيمات النقل الأمينى الاسبرتيت والألانيين أمينوترانسفيريز ونشاط إنزيم الفوسفاتيز الحامضى ومستوى الألبيومين والبروتين الكلى وذلك من ناحية المعايير البيوكيميائية لوظائف الكبد ، وكذلك بالنسبة لتركيز حمض اليوريك والكرياتينين من ناحية المعايير البيوكيميائية لوظيفة الكليه. وكانت هذه التأثيرات متوافقة مع نتائج الفحص الهستوباثولوجى لأنسجة الكبد والكليه. وبطريقة مماثلة فقد أحدث الأبامكتين تأثيرا ضارا على بعض مؤشرات الدم (عدد كرات الدم الحمراء والبيضاء وتركيز الهيموجلوبين) وكذلك أحدث نقص غير سوى فى مقدار سكر الدم. على الجانب الأخر لم يتم ملاحظة الأضرار سالفة الذكر فى الفئران المعاملة بالمبيد الحيوى (*B. t.*) .