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Toxicity Assessment of Synthetic Pyrethroids (Lambda Cyhalothrin) on the Liver and Kidney Organs of Male Wistar Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FIO, O. O. Fadina and O. O. Fayinminnu designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript and managed the analyses of the study. Author FIO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Humans and animals are occasionally and unintentionally exposed to lethal and sub lethal doses of pesticides stemming from its various uses to control pests both in agriculture, homes, gardens and public health. The use of pyrethroid products has grown and continues to grow due to the suspension of some organophosphorus and organochloride products. This current study evaluated the toxic effects of lambda-cyhalothrin (LCT) on hematological and histopathological changes in the liver and kidney organs of rats after sub chronic exposure.

Study Design: Completely randomized design (CRD) with 5 treatments replicated 5 times.

Place and Duration of Study: Department of Crop Protection and Environmental Biology, Faculty of Agriculture and Forestry, University of Ibadan, Nigeria, between July and August, 2015.

Methodology: Twenty-five 7-week-old male Wistar rats were randomly assigned to five groups. The control (group 1) received distilled water, while experimental groups 2, 3, 4 and 5 received by

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gavage 25, 50, 75 and 100 mg/kg body weight, respectively LCT over a period of five weeks. Hematological and histopathological studies were carried out on the blood and organs of interest, respectively on termination of the experiment.

Results: There was a dose-related reduction of white blood cell count from 3.25 ± 0.22 (control) to 3.00 ± 0.62 (100 mg/kg), and severity in alteration of the micro anatomy of the liver and kidney with increase in LCT concentration in the treated animals. The results showed necrosis and vacuolar changes in the hepatocytes and congestion of interstitial blood vessels. Also observed was a significant change in the body weight of the wistar rats after the 5th week of treatment with an average weight of 198 kg, 196 kg, 194 kg, 186 kg, 160 kg for control, 25 mg/kg, 50 mg/kg, 75 mg/kg and 100 mg/kg treatment respectively.

Conclusion: lambda-cyhalothrin is highly toxic (even at the lowest dose in this experiment) and may cause cell damage, organ failure, anaemic conditions and reduce immunity.

Keywords: Pyrethroid; hepatocytes; necrosis; toxicity; wistar rat; liver; kidney.

1. INTRODUCTION

Although pesticides have largely benefited the human life through enhancement of agricultural products and controlling infectious diseases, however, their extensive use in turn, has offended human health from occupational or environmental exposures [1]. Long-term contact to pesticides can harm human life and can disturb the function of different organs in the body, including nervous, endocrine, immune, reproductive, renal, cardiovascular and respiratory systems [1]. Pesticides constitute the most widespread environmental contaminants due to their ubiquitous use in all aspects of human endeavors. Pesticide residues are often reported in foods and known to gain entry into the human body through the consumption of such foods. The people who use pesticides or regularly come in contact with them must understand the relative toxicity and potential health risk associated with these pesticides. All directions, restrictions and precautions on pesticide labels should be observed. Also, pesticides should only be used when absolutely necessary.

Pyrethroids are derived from the naturally occurring pyrethrums, which in turn are the oleo-resin extracts of dried chrysanthemum flowers. Their persistence in the environment is in the order of weeks, unlike organochlorines, which persist for years [2]. Insecticidal products containing pyrethroid have widely been used for pest control in agriculture, public health, homes and gardens [3]. In agriculture, cotton, cereal, hops, ornamentals, potatoes and vegetables are the target crops to control aphids, coleopterous and lepidopterous pests [4]. It is an important tool in public health management to control

cockroaches, mosquitoes, ticks and flies, which can act as disease vectors.

Lambda-cyhalothrin (trade names Excaliber, Karate, Grenade, Lara force, Kombact, Warrior) penetrates the insect cuticle, disrupting nerve condition within minutes, this leads to loss of muscular control, paralysis and eventual death [5]. It was found that lambda-cyhalothrin is moderately toxic for mammals [6-8] Similar to other compounds from the pyrethroid family, the toxicity of lambda-cyhalothrin could vary depending on both its concentration and the nature of used solvent [9]. Adverse changes in liver and kidney tissues of test animals have also been observed on cypermethrin (pyrethroid) – treated male rats [10].

Therefore, the use of lambda-cyhalothrin domestically and in agriculture necessitated the study of its toxicity. Due to its widespread use in agriculture and public health, the present study is aimed at assessing the toxicity following sub chronic exposure of sub lethal doses.

2. MATERIALS AND METHODS

2.1 Experimental Materials

A total of 25 individual male of *Rattus norvegicus* with weights ranged from 100–150 g were used for this study. Wistar rats were procured from the Animal House of the Department of Physiology, College of Medicine, University of Ibadan, Nigeria. The rats were acclimatized for three weeks before the commencement of the treatments. The rats were fed on growers mash throughout the duration of the study and the feed was purchased from a local agrosshop. Water and feed were supplied *ad libitum*. All experimental

animals were handled in accordance with the guidelines for care and use of laboratory animals.

2.2 Dilution of Lambda-cyhalothrin (LCT) Pesticide

The pesticide LCT was mixed with a vehicle (water). The concentration of the active ingredient in Kombat is 25 g/L (on label), this is also equivalent to 25,000 mg/L. A 2 mls of the pesticide solution was taken and distilled water added to make it up to 500 mL, this gave a solution of the active ingredient in 1,000 ppm. These concentrations were determined using the formula below as described by [11].

$$C_1V_1 = C_2V_2$$

Where;

C_1 = initial concentration of stock
 V_1 = volume of stock used
 C_2 = desired concentration
 V_2 = desired volume

From this stock solution, the following treatments were taken and distilled water added to make it up to 250 mL.

Treatment 4: 6.25 mL equivalent to 25 mg/L
Treatment 3: 12.5 mL equivalent to 50 mg/L
Treatment 2: 18.75 mL equivalent to 75 mg/L
Treatment 1: 25 mL equivalent to 100 mg/L

2.3 Experimental Set Up/Toxicological Study

The experiment was laid out in a completely randomized design (CRD) with 5 treatments replicated 5 times. The 25 Wistar rats were divided into 5 groups of 5 rats each. The various levels of the pesticide formed the treatment with a control group (no pesticide). The treatment levels were:

T4= 25 mg/kg of LCT
T3= 50 mg/kg of LCT
T2= 75 mg/kg of LCT
T1= 100 mg/kg of LCT

All doses (treatments) were administered daily (in the mornings) by oral gavage (with a 2 ml syringe and cannula) for a period of five weeks. Animals were weighed weekly. At the end of the experiment, animals were sacrificed by cervical dislocations. The organs of interest (liver and kidney) were carefully dissected out and weighed.

2.4 Data Collected

The animals were weighed weekly in order to determine weight gain/loss also; The feed given was weighed in order to ascertain the daily feed intake. Physical observations such as shyness, behavioral pattern of the rats, signs of pesticide toxicity such as tremors, loss of appetite, muscle jerking, constricted pupils, vomiting etc. [12] were recorded per animal in each treatment.

2.5 Histopathological Analysis

On termination of the experiment, all the surviving Wistar rats were sacrificed and organs of interest (liver and kidney) were harvested via cervical dislocation. In preparing the animal tissues (liver and kidney) of each rat for microscopic examination, histological procedures were followed in a stepwise protocol thus: fixation, dehydration, clearing, infiltration, embedding, blocking, sectioning and staining [13-15].

2.6 Statistical Analyses

Data obtained from the study were subjected to one-way analysis of variance ANOVA (SAS Version 9.2, 2002; 2003), while group means were compared for significant differences at 95% confidence level ($p = .05$) [16]. The results are presented as mean \pm standard error of the mean (SEM).

3. RESULTS AND DISCUSSION

3.1 Behavioral/Morphological Responses

All the rats were observed to rub their lip regions and faces with their fore limb after treatment administration. General loss of appetite was also noticed in all treated rats. Obvious behavioral response to pesticide toxicity (nasal discharge and paralyses) was evident amongst most of the LCT treated rats. A significant dose- dependent decrease in body weight was observed for rats treated with LCT when compared with control.

3.2 Hematological and Serum Biochemistry Results Examination

Results showed a significant dose dependent decrease in white blood cell count and hemoglobin with increase in concentration of LCT. Also the Eosinophil value for the control was significantly ($P = .05$) lower than those of the

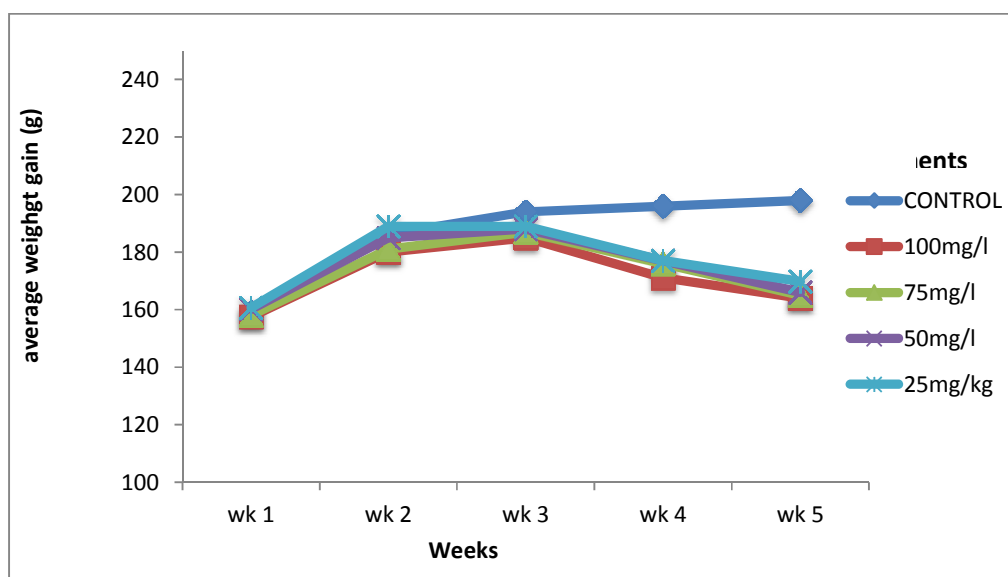


Fig. 1. Effects of varying concentrations of Lambda-cyhalothrin on average weight (g) of *Rattus norvegicus*

Table 1. Effects of varying concentrations of Lambda-cyhalothrin on blood sample parameters of wistar rats

Treatments(mg/kg)	ALB	HB(g/dl)	RBC($10^6/\mu\text{l}$)	WBC	Eosinopil(%)
100	3.72±2.12a	13.95±0.71a	7.95±2.12a	3.00±0.62ab	4.20±0.87a
75	3.67±2.35a	14.10±0.78a	8.04±2.35a	3.00±1.18ab	4.50±0.65a
50	3.87±2.02a	14.10±0.67a	8.06±2.02a	2.60±0.11a	4.25±0.85a
25	3.75±2.95a	14.55±0.98a	8.11±2.95a	2.70±0.35a	3.55±0.48a
control	3.65±0.50a	15.3±0.17b	8.87±0.50b	3.25±0.22b	1.25±0.48b

* Means within the same column followed by the same letter(s) are not significantly different at $P = .05$ using DMRT

HB = Hemoglobin, RBC = Red Blood Cell counts, ALB = Albumin, WBC = White Blood Cell count

LCT treated rats. There was no significant difference ($P = .05$) in albumin between the control and LCT treatments.

3.3 Histopathological Examination

Result from observations conducted on the liver revealed a slightly enlarged liver, thinning of hepatic cord, vacuolar change of hepatocytes, random foci of single-cell, hepato-cellular necrosis and hyperplasia of kupffer cells in all LCT treated rats which became more obvious with increase in LCT dose. The section of the control liver generally exhibited no visible lesion on close observation (Fig. 2)

Kidneys of lambda-cyhalothrin treated *Rattus norvegicus* showed cloudy swelling of tubular epithelial cells, congestion of interstitial blood vessels and flattened epithelium in the renal cortex when compared with the control. These

also became more conspicuous with increase in concentration of lambda-cyhalothrin in the examined kidney. The control kidneys appeared normal with no gross visible lesions and necrosis (Fig. 3).

4. DISCUSSION

This present study showed that exposure/ oral administration of Lambda cyhalothrin at varying concentrations of 100, 75, 50 and 25 mg/kg for five weeks to male Wistar rats induced body weight loss, reduction in the white blood cell count and hemoglobin, and deleterious effects on the liver and kidney organs.

There was a significant decrease in weight of all LCT treated rats with 100 mg/kg LCT recording the highest weight loss. This is often associated with pesticide toxicity.

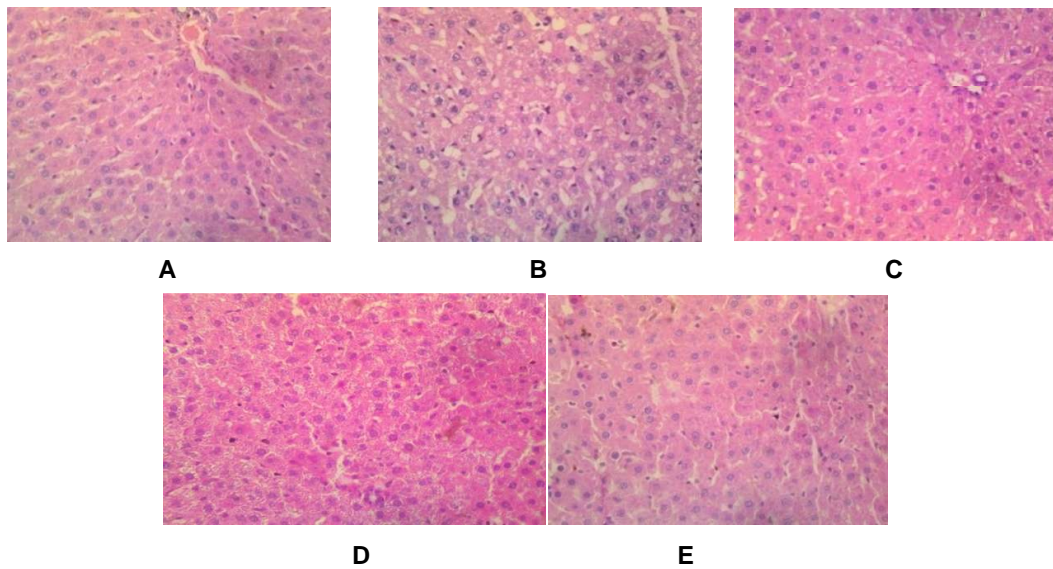


Fig. 2. Histological section of liver of *Rattus norvegicus*

A– 100 mg/kg Few foci of moderate thinning of hepatic cords, multiple foci of mild vacuolar change of hepatocytes. There were a few random foci of single-cell hepatocellular necrosis. B– 75 mg/kg. Few foci of moderate thinning of hepatic cords, multiple foci of mild vacuolar change of hepatocytes. There are a few random foci of single-cell hepatocellular necrosis. C– 50 mg/kg. Hepatic plates closely-packed with few foci of mild vacuolar change of hepatocytes. D– 25 mg/kg. The hepatic plates were closely-packed. No visible lesion. E– Control. The hepatic plates are closely-packed. H& E Magnification x400

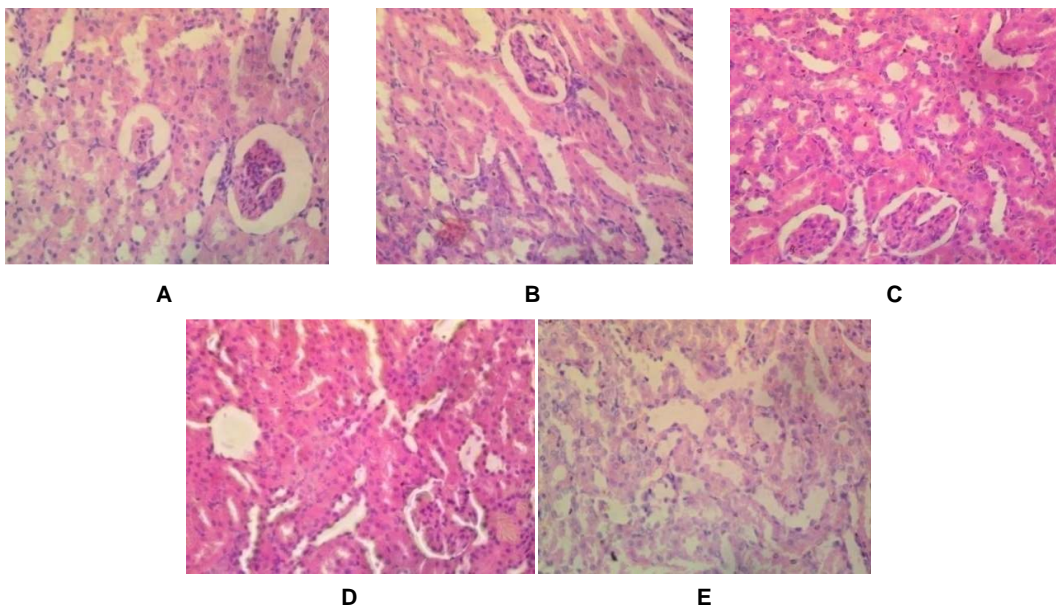


Fig. 3. Histological section of kidney of *Rattus norvegicus*

A– 100 mg/kg. Few foci of mild cloudy swelling of tubular epithelial cells. B– 75 mg/kg. Moderate congestion of renal interstitial blood vessels. No visible lesion (NVL) with glomeruli and tubules. C– 50 mg/kg. Moderate congestion of renal interstitial blood vessels. NVL with glomeruli and tubules. D– 25 mg/kg. There was mild congestion of interstitial blood vessels. NVL with glomeruli and tubules. E– Control. No Visible Lesion; normal glomeruli, tubules and renal interstitium. H& E Magnification x400

The liver is one of the largest organs and carries out the most complex biological function in the body. It secretes bile, synthesizes proteins, metabolizes nutrients, hormones and drugs and detoxifies noxious endogenous and exogenous substrate. Any toxic substance entering the body, such as LCT, would undergo biochemical transformation in the liver where it is detoxified by being metabolized. Overloading of the detoxification pathways leads to a build-up of toxins in the body leading to higher levels of free radicals, excess of which may damage the liver cells [17].

The Sub-chronic exposure of the rats to lambda-cyhalothrin resulted in the alteration of the micro anatomy of the liver. This alteration included vacuolar changes of hepatocytes and hepatocellular necrosis, and becomes more conspicuous with increase in LCT concentration. Also, the micro anatomy of the kidney was altered with cloudy swelling of tubular epithelial cells, congestion of interstitial blood vessels although there were no visible lesions in both the liver and kidney. This is in line with findings of [18] who recorded adverse changes in liver tissues of test animals that have been treated with cypermethrin. [10] Also revealed was a significant increase in weight of kidney of rats treated with synthetic pyrethroid (cypermethrin).

The experiment showed significant dose dependent decrease in white blood cell counts, red blood cell counts and hemoglobin with increase in concentration of LCT. This conforms to the work of [19] who reported that oral ingestion of lambda-cyhalothrin significantly decreased the count of RBCs and WBCs content of treated rat relative to control and this probably explains the effect of lambda cyhalothrin on the erythropoiesis and the destruction of cells. This decrease in the WBC could leads to reduced body system immunity, anemic conditions and other health challenges in animals exposed to LCT.

The elevated Eosinophil (which was produced by the white blood cell for combating infections/toxin in the body) level recorded in the treated rats when compared with the control is an indication of the toxicity of LCT.

5. CONCLUSION

The experiment suggested a dose-dependent toxicity on the selected parameters. Lambda-cyhalothrin is highly toxic (even at the lowest

dose in this experiment) and may cause cell damage, organ failure, anaemic conditions and reduce immunity upon continuous exposure thereby affecting the overall health and wellbeing of the LCT- treated animals.

ETHICAL ISSUE

All animals were handled in accordance with the guidelines for care and use of laboratory animals as well as specific national laws where applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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