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Original Research Article

# EFFECTS OF DICHLORVOS INHALATION ON THE KIDNEY IN ADULT WISTAR RATS

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**Abstract:** Dichlorvos, (2, 2, dichlorovinyl dimethyl phosphate; DDVP), is an organophospharous compound used as insecticides and pesticides in homes and farms. It constitutes the active ingredient of *Ota-piapia* or *Madarar piapia,* a locally formulated insecticide in Nigeria. It is absorbed into the body via inhalation, dermal or oral routes and metabolized by the liver and excreted by the kidney. The frequency of renal failure is on the increase. The study aimed at assessing the effects of dichlorvos on the histology of the renal cortices in Adult Wistar Rats. Twenty - five adult wistar rats weighed about 195 – 400g were randomly selected and divided into five groups, two positive and negative groups and three treated groups exposed to 11.25mg/m$^3$, 7.50 mg/m$^3$, and 3.75 mg/m$^3$, of dichlorvos in 96% (purity) ethanol solution and experimented for 28 days. The animals were sacrificed twenty four hours after the last exposure, the blood and the kidney tissues were collected for serum and histopathological analyses. The slides were observed under light microscope while the blood was run for serum analysis. One way analysis of variance (ANOVA) followed by Post – hoc test (*Tukey*) was conducted for the serum analysis. Graded degenerations in kidney cellularity were observed. There was significant difference ($P < 0.001$) in the serum electrolytes across the groups. Prolonged use of dichlorvos could be injurious to the architecture of renal cortex that might lead to renal failure.

**Keywords*:*** Dichlorvos, inhalation, kidney, serum electrolytes

**Introduction:** Toxicity in human is a threatening truth and much more than any disease caused by organism as toxic substances are everywhere in air, in water and in food. Many compounds which are essential to use for human welfare are at the same time injurious when viewed from safety point. Some compounds are not directly used by humans but indirectly they enter human (through food chain) and induce injuries [1].

The primary function of kidney is the maintenance of water, electrolyte and acid-base

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haemostasis. Other functions include the excretion and elimination of many toxic waste products among others [2]. The nephrons are the functional units of the kidney and are composed of renal corpuscles (glomeruli and renal corpuscle) and renal tubules. The nephrons are involved in osmoregulation and excretion through the process of ultrafiltration, selective re-absorbtion and secretion of some of the excretory substances directly from the blood into the glomerular filtrate [3]. For this, injury to the kidney will affect its metabolic function involved in the excretion of waste product which in turn may affect general body functions in events if renal failure occurs.

Dichlorvos (2, 2 dichlorovinyl dimethyl phosphate), is an organophosphate with strong pesticide activity [4]. Dichlorvos (DDVP), has demonstrated alteration of the microanatomy of some internal organs of exposed mammals. Deleterious effect of DDVP on the heart, brain and other soft tissues in rats was reported following dermal exposure of rats to DDVP [5]. Similarly, it was reported that enlarged bronchial associated lymphoid developed in the lungs tissues of rats chronically exposed to inhale DDVP, as well as the necrosis and scar formation in the liver of same animals [6]. Other reports showed alterations in the haematological parameters of rats treated with inhalational DDPV [7]. In Nigeria, the availability, low cost and accessibility of dichlorvos commonly called Ota piapia used by low-income group has been confirmed as the preponderant active pesticide ingredient [8]. Like other organophosphates, the mechanism of action for the dichlorvos is mainly by blocking of acetylcholinesterase – an enzyme which in turn decomposes acetylcholine [9, 10]. Overdose of dichlorvos leads to symptoms which include weakness, headache, and tightness in chest, blurred vision, salivation, sweating, nausea, vomiting, diarrhea, respiratory failure, and abdominal cramps being an acetylcholinesterase inhibitor [11]. Dichlorvos is mainly metabolized by esterase to dimethylphosphate and dichloroacetaldehyde. Dimethylphosphate is excreted in the urine, while dichloroacetaldehyde is rapidly metabolized via two pathways to dichloroethanol glucuronide, hippuric acid, urea and carbon dioxide, and excreted in the urine and expiration [4]. The basis for DDVP toxicity was reported to be oxidative stress through generation of reactive oxygen species (ROS) as observed in laboratory animals [12, 13]. Excess ROS production may lead to lipid peroxidation as well as damage to other macromolecules [14, 15].

Late in the 1960s, design of resin strips or application rates of dichlorvos in liquid or fogger formulations was guided by the goals of achieving dichlorvos concentrations in the air of at least 0.015 mg/m$^3$ for a period of several hours; this goal to achieve good kills of nuisance insects was balanced against the rule of thumb that concentrations below 0.25 mg/m$^3$ provided an adequate margin of safety for human health [16].

Although many researches were conducted on the toxic effect of dichlorvos, present research aims at assessing the consequences of indiscriminate use of dichlorvos through inhalation on the histology and serum electrolytes of the renal cortex.

**Methods:** ***Animals*****:** Twenty-five apparently healthy rats of Wistar strain Consisted of both sexes and weighed about 195 – 400g were purchased from the Pharmacology Department, Aminu Kano Teaching Hospital (AKTH) and quarantined for a 2 week period. Fabricated Aluminum cage with stainless wire lids and saw dust beddings were used to house the rats in biologically clean rooms, a 12 hour light-dark cycle, average air temperature and relative humidity. The cages were cleaned up approximately once every week. The animals were fed with pelleted rodent chow, (*Vital feeds*, Nig. Ltd) and deionized filtered tap water were made available every time except during exposure. The study was conducted under the federal guidelines for care and use of animal and supervision of University committee on laboratory ethics.

**Procurement of the Chemical and Samples Preparation:** A stock concentration of 1000 g/l of dichlorvos (Delvap©) was purchased from the vendors of insecticides, pesticides and other Agro Allied Chemicals at Sabongari Market, Kano. The chemical was taken to the

Department of Industrial Chemistry Laboratory of the institution for the preparation of 11.75 mg/l, 7.5 mg/l and 3.75 mg/l in ethanol solution (96% purity) which was the 75%, 50% and 25% of the lethal concentration LC50 (15mg/l) of dichlorvos [17].

**Animal Grouping and Exposure:** Five poorly ventilated 1m x 1m cubed wooden boxes labeled A, B, C, D and E, each with a rectangular opening covered with a sliding glass pane measured about 0.2m x 0.1m for entrance from the tops of the boxes were constructed for the exposure of the animals. The animals were then divided into five groups (i.e. I, II, III, IV & V) each contained five member with at least one of the congeners. About 2mls each of the graded solutions were drawn separately using 4mls hypodermic syringes and then sprayed into boxes every day before exposure. The animals in groups III, IV & V were exposed into the boxes sprayed with 11.25 mg/l, 7.5 mg/l, and 3.75 mg/l concentrations of the prepared solutions so as to create air of assumed equal concentrations as the solutions within the boxes. The animals were exposed for two hours daily for 28 days. The remaining two groups (i.e. I and II) were exposed to ambient air and ethanol solutions as positive and negative controls respectively. To maintain equal distribution of the chemicals exposed the animals in the boxes throughout the period, about 2mls of each of the solution was soaked in a cotton wool that was attached to a nylon string of about 10cm long and suspended from the top of the boxes using the margins between the sliding glass cover and the openings of the boxes as attachments.

**Animals Sacrifice and Sample Collection:** The animals were humanely sacrificed through cervical decapitation using a sharp dissecting knife. About 2mls of the blood samples were collected in heparinized tubes and centrifuged at 5000 rpm for 10mins. The serum was separated and stored at -70$^0$ C until use. The samples of the kidney tissues from each group were harvested and preserved in 10% formalin. Thereafter, the samples were made to undergo routine histological technique for H&E stain.

**Histology and Histopathology:** The stained sections were examined with the light microscope (Motic Photomicroscope, Xiamen, China) for histopathological evaluation. Photomicrographs were taken with a *Celestron*© Digital Microscope Imager (USA) with an inbuilt x15 magnifying lens at a total magnification of x150 and x600 respectively.

**Measurement of Renal Function Test:** The serum was evaluated for the electrolytes ($Na^+$, $K^+$ and $Cl^-$), urea and creatinine. Serum creatinine was measured as described by Bartels and Bohmer[18]. The urea was determined using urease enzyme kit modified by modified Berthelot[19]. While the serum the $Na^+$ and $K^+$ were determined using modified methods of Maruna and Trinder [20, 21]. The Cl- was determined using the modified method of Skeggs and Hochestrasser [22]. Absorbance was measured using Cary® 50 UV-Vis spectrophotometer.

**Statistical Analysis:** The values of the serum blood electrolytes were expressed as Mean±SEM and then subjected to one way analysis of variance followed by Tukey's multiple comparison tests. The statistical analysis was conducted using Minitab version 16.0 Statistical Package. Values of $P$ □ 0.05 were considered significant.

**Results and Discussion: Table 1. Serum Electrolytes Analysis of Adult Wistar Rats after Exposure to Graded Doses of Dichlorvos**

| Electrolytes | Positive Control | Negative Ethanol | Dichlorvos (11.25mg/m$^3$) | Dichlorvos (7.5mg/m$^3$) | Dichlorvos (3.75mg/m$^3$) |
|---|---|---|---|---|---|
| $Cl^-$ | 54.89±1.00 | 83.84±0.78* | 65.63± 1.22* | 127.73±0.65* | 99.30±1.12* |
| $K^+$ | 6.04±0.32 | 11.38±0.91* | 10.06±0.82* | 6.90±0.60* | 7.87±0.66* |
| $Na^+$ | 87.73±0.55 | 77.80±1.08* | 60.09±1.07* | 176.23±0.63* | 74.62±0.978* |
| UREA | 3.31±0.86 | 7.47±1.04* | 1.71±0.90* | 11.49±0.58* | 3.84±1.19** |
| CREATININE | 43.65±0.36 | 56.20±0.83* | 50.25±0.87* | 64.16±0.81* | 40.41±0.99* |

***P* < 0.001; ****P* > *0.001***

**Effect of Dichlorvos on the Serum Renal Electrolytes:** The result in table 1 showed the Mean±SEM of the serum renal electrolytes of adult wistar rats exposed to graded doses of dichlorvos in ethanol solution. It was evidently clear that there was statistically significant ($P < 0.001$) difference in the mean serum electrolytes between the treated groups and the control groups, except for the urea in group V where the $P > 0.05$.

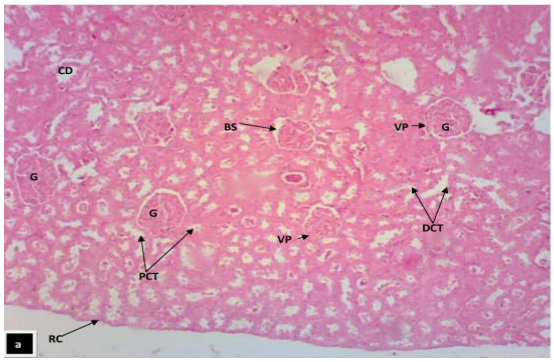


**Figure 1a:** H&E photomicrograph of renal cortex of adult wistar rat exposed to ambient air (positive control) at x150. **BS**= Bowman's capsular space; **CD**; Collecting Tubule; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule; **RC=** Renal Capsule **VP**= Vascular Pole.

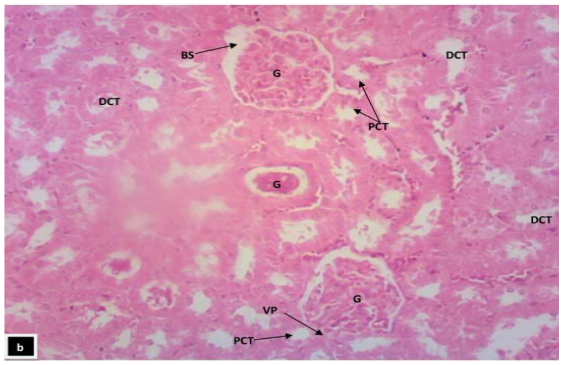


**Figure 1b:** H&E photomicrograph of renal cortex of adult wistar rat exposed to ambient air (positive control) at x600. **BS**= Bowman's capsular space; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule; **VP**= Vascular Pole.

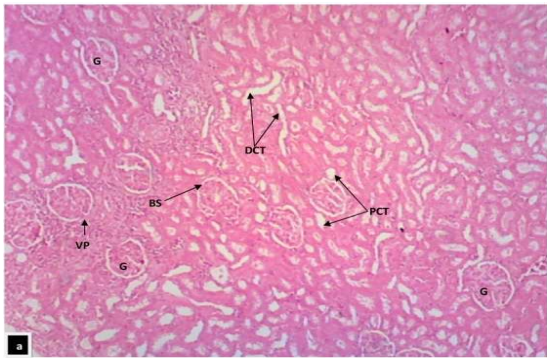


**Figure 2a:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 95% ethanol negative control) at x150. **BS**= Bowman's capsular space; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule; **VP**= Vascular Pole.

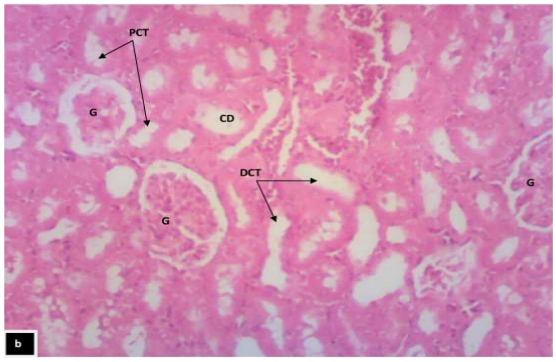


**Figure 2b:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 95% ethanol negative control) at x600. **CD**; Collecting Tubule; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

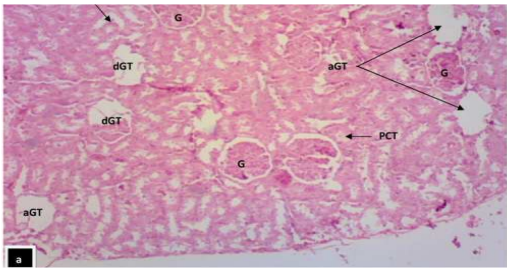


**Figure 3a:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 11.25mg/m$^3$ dichlorvos at x150. **aGT**= Degenerated Glomerulus; **dGT**= Degenerating Glomerulus; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

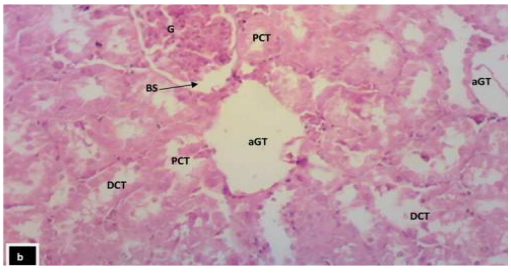


**Figure 3b:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 11.25mg/m$^3$ dichlorvos at x600. **aGT**= Degenerated Glomerulus; **BS**=Bowman's Capsular Space; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

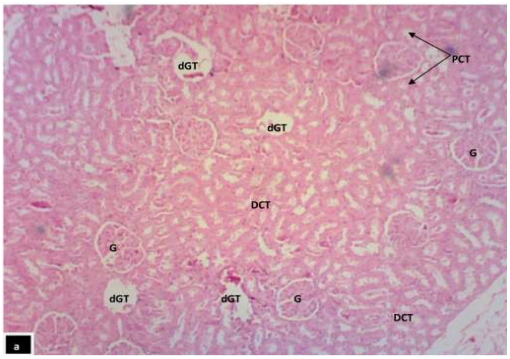


**Figure 4a:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 7.50mg/m$^3$ dichlorvos at x150. **aGT**= Degenerated Glomerulus; **dGT**= Degenerating Glomerulus; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

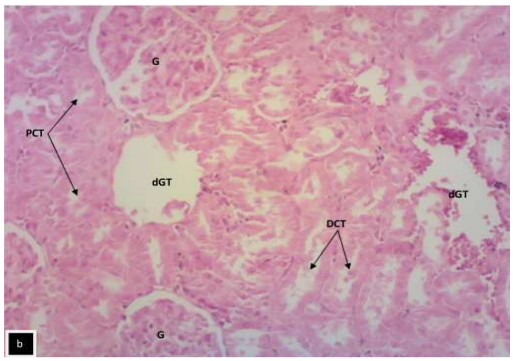


**Figure 4b:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 7.50mg/m$^3$ dichlorvos at x600. **aGT**= Degenerated Glomerulus; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

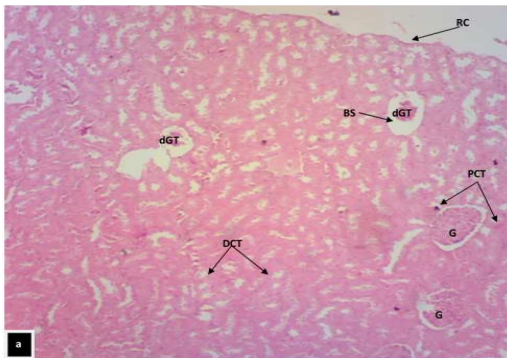


**Figure 5a:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 3.75mg/m$^3$ dichlorvos at x150. **BS**= Bowman's capsular space; **dGT**= Degenerating Glomerulus; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule; **RC=** Renal Capsule.

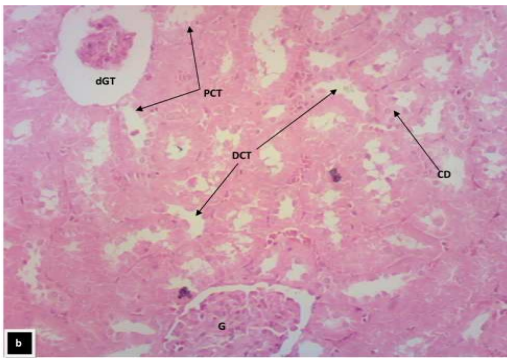


**Figure 5b:** H&E photomicrograph of renal cortex of adult wistar rat exposed to 3.75mg/m$^3$ dichlorvos at x600. **CD** = Collecting Duct; **dGT**= Degenerating Glomerulus; **DCT**= Distal Convoluted Tubules; **G**= Glomerulus; **PCT**= Proximal Convoluted Tubule.

**Effects of Dichlorvos Inhalation on the Histology of the Kidney:** The histology of the kidneys of normal adult wistar rats used as positive and negative control groups showed the architecture of normal glomeruli (G) surrounded by Bowman's capsular spaces (BS), which enclosed the glomeruli and vascular poles (VP) that attached to the glomeruli within the capsule (Fig. 1a & b). The proximal convoluted tubules (PCT) were intimately attached close to the capsules bearing circularly arranged cuboidal cells featuring lumina of virtually equal sizes. The rest of the renal tubules were also interspersed within the renal parenchyma at intervals (Fig. 1b & b) and featured lumina of different capacities lined by cuboidal epithelia. The sections of the renal cortex treated with 11.25mg/m$^3$ (75% LC50) dichlorvos showed increase renal capsular sizes, reduction in glomerular cellularity, and different stages of glomerular degeneration (dGT & aGT) (Fig. 3a & b). At higher resolution, the section showed mild degeneration of the renal tubular architecture of (Fig. 3b) and increase in lumina diameters. Similar results were observed in the group treated with 7.5mg/m$^3$ (50% LC50); except for the fact that the severity of the degeneration in the glomerular tufts cellularity (dGT) and renal tubular lumina (Fig. 4a&b) were less intense compared to the groups treated

with higher doses. In the sections of the rats treated with 3.75mg/$m^3$ (25% LC50) (Fig. 5a & b), the results were also similar, however with less intensity.

**Discussion:** Many pesticides can cause some toxic and adverse effects on the kidney tissues [23]. Kidney is one of the targets organs of experimental animals attacked by organophosphate compounds [24, 25]. The nephron is the functional unit of the mammalian kidney that functions in the ultrafiltration of blood, removal of metabolic waste and subsequent formation of urine [3]. Prolonged exposure to dichlorvos significantly alters the mean serum renal electrolytes concentrations in the treated groups compared to the control except for urea in group V of the animals treated with 3.75mg/$m^3$ dichlorvos. The results obtained in the present study contradicted the finding of Ambali *et al.* [26] which reported that no significant increase in the serum concentrations of $Na^+$, $K^+$ and $Cl^-$ were observed in rats following oral treatment with a pesticide, chlorpyrifos. The reason for increase in $Na^+$, $K^+$ and $Cl^-$ concentrations in the dichlorvos treated groups compared to the normal groups was that DDVP like other organophosphate pesticides and their metabolites are generally eliminated through urine and are likely to affect nephrons [27]. Being the first part of nephron, glomerulus is directly exposed to nephrotoxins. This could have led to nephrotoxicity on the kidney which is capable of inducing glomerular injury. As a consequence, release of metabolic waste product such dimethyl phosphate, a product of dichlorvos metabolism over a period of time overloading of the kidney and caused loss of physiologic functions of the glomeruli, thereby making it ineffective for selective reabsorption and ultrafiltration.

Urea, uric acid and creatinine levels are kidney function parameters [24, 25, 28]. Pesticides can alter plasma urea, and creatinine levels [24, 29, 30]. In this study, dichlorvos exposure increased in the urea and creatinine levels in the treated rats when compared to control rats. The finding was in line with the result obtained by Ojo *et al.* [31] where significant increase in urea and creatinine level was reported following dichlorvos treatment. This was attributed to be due to oxidative stress resulting from reactive oxygen species (ROS) generated by DDVP. These species might have as well caused cellular damage that resulting in cell shrinkage and degeneration of the glomerular tuft and the renal tubules diameters. This in turn might have affected glomerular function of ultrafiltration and selective reabsorption thereby leading to higher concentration of virtually all the serum electrolytes.

The histopathological examination of the photomicrographs of the renal cortices in adult wistar rats treated with graded doses of dichlorvos resulted in histological changes in the Kidney including reduction in cellularity, degeneration of glomerular tufts. In a similar study conducted by Luty *et al.* (1998) using inhalational method of exposure, had reported both histological and ultra-structural studies of the kidney showed considerably widened spaces between the convoluted tubules infiltrated with lymphocytes, implying a possible immune reaction to the exposure to dermal DDVP for four weeks.

Being the cheapest, most affordable and readily available organophosphate, dichlorvos exposure is very common especially among the lower class of Africa. It is evident therefore that prolong exposure could be damaging to the histology of the kidneys and cause increase in the serum renal electrolytes. Excessive lost of renal electrolytes can put the users at the higher risk renal failure.

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**Conflict of interest:** The authors declared no conflicts of interest.

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