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Toxicological Effects of 2-2, Dichlorovinyl Dimethyl Phosphate on Lipid and Glucose Levels in the Blood of New Zealand White Rabbits by Inhalation Route of Administration

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Abstract

Background: Dichlorvos, a widely used organophosphate pesticide, is known for its acute cholinergic toxicity, but less is understood about its chronic metabolic effects. This study investigated the impact of prolonged dichlorvos exposure on serum glucose and lipid profiles in rabbits, focusing on its potential cardiometabolic implications. **Methods:** Thirty-six male New Zealand White rabbits were randomly assigned into nine groups (n = 4 per group) comprising oral, inhalation, and control groups for 30, 60, and 90 days. A sublethal dose of dichlorvos (0.05 mg/m^3; 10% of LD_{50}) was administered orally or by inhalation daily. Serum fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C) were analyzed using standard biochemical methods. **Results:** FBG was significantly reduced in exposed groups across all durations ($p < 0.05$). TC, LDL-C, and VLDL-C were significantly elevated, with oral exposure producing stronger effects at later time points. HDL-C initially increased at 30 days but was markedly reduced by 90 days ($p < 0.001$), particularly in the inhalation group. TG levels remained largely unchanged across groups. **Conclusion:** Chronic dichlorvos exposure disrupts glucose and lipid metabolism, promoting a pro-atherogenic lipid profile and sustained hypoglycemia, thereby increasing the risk of cardiometabolic disorders. These findings raise concerns over the health risks of prolonged pesticide exposure and highlight the need for stricter regulation and safer alternatives.

Keywords: *Dichlorvos, organophosphate, glucose metabolism, lipid profile, rabbits, chronic exposure*

1.0 INTRODUCTION

Dichlorvos (2,2-dichlorovinyl dimethyl phosphate; DDVP) is an organophosphate insecticide widely marketed under trade names such as Sniper, Nuvan, Vapona, and Nogos. In Nigeria, it is commonly sold by Swiss-Nigeria Chemical Company under the name "Sniper" and is widely used for agricultural and domestic pest control. Dichlorvos is a colorless to amber liquid with a boiling point of 140 °C at 2.7 kPa, molecular formula $C_4H_7Cl_2O_3P$, molecular weight 220.98 g/mol, vapor pressure 1.2×10^{-2} mmHg at 20 °C, and density of 1.415 g/mL at 25 °C. Based on the World Health Organization (WHO) classification, dichlorvos is categorized as a Class Ib "highly hazardous" pesticide, reflecting its substantial toxicological risk to humans and animals [1].

Despite this classification, dichlorvos remains widely used in many developing countries, often without adequate regulation, quality control, or adherence to occupational safety standards. The Occupational Safety and Health Administration (OSHA) has set an exposure limit of 1 mg/m^3, yet improper handling, storage, and indiscriminate use often result in exposures that exceed this threshold. Acute and chronic intoxications have been reported globally, with an estimated 3 million cases of organophosphate poisoning and over 25,000 deaths annually [1]. In Nigeria, misuse of dichlorvos has been associated not only with unintentional poisonings but also with suicides and homicides, making it both a public health and forensic concern.

The primary mechanism of dichlorvos toxicity is through irreversible inhibition of acetylcholinesterase (AChE), leading to excessive accumulation of acetylcholine at cholinergic synapses. This overstimulation of muscarinic and nicotinic receptors produces a wide spectrum of toxic effects involving the respiratory tract, cardiovascular system, liver, kidneys, and central nervous system [2,3] Beyond acute cholinergic crises, emerging evidence suggests that chronic dichlorvos exposure disrupts intermediary metabolism, particularly glucose and lipid homeostasis, which are critical determinants of cardiovascular and metabolic health [4,5].

Glucose metabolism is tightly regulated by hepatic and pancreatic functions, with the liver playing a central role in glycogen storage, gluconeogenesis, and energy supply. Toxic insults such as pesticide exposure may impair hepatic glucose regulation, leading to hypoglycemia. Indeed, hypoglycemia has been reported in pesticide-induced hepatotoxicity due to impaired gluconeogenic enzyme activity and depletion of glycogen reserves [6,7]. On the other hand, lipid metabolism disturbances, including hypercholesterolemia and elevated low-density lipoproteins (LDL-C), have been implicated in the pathogenesis of atherosclerosis and cardiovascular diseases [8,9]. Alterations in serum lipids not only reflect hepatic dysfunction but also serve as early biomarkers of cardiometabolic risk [10,11]

Several studies have linked organophosphate exposure to dyslipidemia and impaired glucose regulation. For example, Arthur et al. [3] reported significant disturbances in lipoprotein profiles in rats treated with dichlorvos, while Gourdarz et al. [6] observed suppression of blood glucose in dichlorvos-exposed mice. However, there is limited evidence on the combined assessment of glucose and lipid indices following chronic inhalation exposure to dichlorvos, despite inhalation being one of the most common routes of human exposure due to its high volatility.

Given the widespread and often indiscriminate use of dichlorvos in Nigeria and other low- and middle-income countries, there is a pressing need to evaluate its long-term toxicological effects on biochemical parameters that are central to metabolic and cardiovascular health. The present study was therefore designed to assess

the impact of chronic inhalation exposure to dichlorvos on serum glucose and lipid profiles in New Zealand White rabbits, serving as a mammalian model. By investigating both hypoglycemic and dyslipidemic outcomes, this study aims to provide insight into the potential role of dichlorvos in the development of metabolic and cardiovascular complications, while contributing evidence for public health regulation and risk assessment.

2.0 MATERIALS AND METHODS

2.1 Experimental Animals

A total of thirty-six (36) male New Zealand White rabbits (*Oryctolagus cuniculus*), two months old and weighing between 1.0 and 1.2 kg, were used for this study. The animals were procured from the Port Harcourt Animal Shelter, Rivers State University, Nigeria. Upon arrival, they were acclimatized for 14 days in a well-ventilated animal house maintained at room temperature under natural circadian rhythm. Rabbits were housed in standard cages and provided with commercial feed (Top Feed Finisher Mash, Sapele, Nigeria) and clean water *ad libitum*.

2.2 Experimental Grouping and Dichlorvos Administration

The rabbits were randomly assigned into nine groups (n = 4 per group) based on exposure route (oral or inhalation) and duration (30, 60, and 90 days), with corresponding controls (Table 1).

Table 2.1: Experimental Grouping of Rabbits

Group	No. of Rabbits	Treatment Description
Control 30 days	4	No dichlorvos exposure for 30 days
Oral 30 days	4	Dichlorvos oral administration daily for 30 days
Inhalation 30 days	4	Dichlorvos inhalation exposure daily for 30 days
Control 60 days	4	No dichlorvos exposure for 60 days
Oral 60 days	4	Dichlorvos oral administration daily for 60 days
Inhalation 60 days	4	Dichlorvos inhalation exposure daily for 60 days
Control 90 days	4	No dichlorvos exposure for 90 days
Oral 90 days	4	Dichlorvos oral administration daily for 90 days
Inhalation 90 days	4	Dichlorvos inhalation exposure daily for 90 days

Total = 36 rabbits

A commercial formulation of dichlorvos (DDVP 1000EC; Swiss-Nigeria Chemical Company, Nigeria) containing 1000 mg/L of 2,2-dichlorovinyl dimethyl phosphate was used. For both oral and inhalation exposures, a sublethal dose equivalent to 10% of the median lethal dose (LD_{50} = 0.5 mg/m^3) was prepared, corresponding to 0.05 mg/m^3.

Oral administration: The diluted solution (0.05 mg/m^3 in 1 mL distilled water) was administered orally to each rabbit once daily using an oral gavage.

Inhalation exposure: The same dose was sprayed into closed exposure chambers. Rabbits were placed inside the chambers for four (4) hours daily, after which they were returned to their housing cages.

Controls: Matched control groups were maintained under identical housing and feeding conditions without dichlorvos exposure.

At the end of each exposure duration (30, 60, and 90 days), one group of exposed rabbits and their corresponding controls were sacrificed for sample collection.

2.3 Laboratory Investigations

2.3.1 Determination of Fasting Blood Glucose

Fasting blood glucose was measured using the glucose oxidase-peroxidase method. In this method, glucose is oxidized by glucose oxidase to produce gluconic acid and hydrogen peroxide. The hydrogen peroxide reacts with 4-aminophenazone and phenol under the catalytic activity of peroxidase to form quinoneimine, a colored compound whose absorbance was measured colorimetrically at 500 nm.

2.3.2 Determination of Total Cholesterol

Total cholesterol was determined using the enzymatic colorimetric method (Randox Laboratory Kits, UK). Cholesterol esters were hydrolyzed by cholesterol esterase, and the free cholesterol was oxidized to yield hydrogen peroxide. This subsequently reacted with phenol and 4-aminoantipyrine in the presence of peroxidase to form quinoneimine, measured at 500 nm.

2.3.3 Determination of Triglycerides

Triglycerides were measured enzymatically. Lipase hydrolyzed triglycerides to glycerol, which was oxidized to produce hydrogen peroxide. The hydrogen peroxide then reacted with 4-aminophenazone and 4-chlorophenol under peroxidase catalysis to form quinoneimine, detected colorimetrically.

2.3.4 Determination of High-Density Lipoprotein Cholesterol (HDL-C)

HDL-C was determined using the precipitation method described by Abell and Kendall [12]. Very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) were precipitated using phosphotungstic acid and magnesium chloride. The supernatant containing HDL was subjected to enzymatic cholesterol determination.

2.3.5 Determination of Low-Density Lipoprotein Cholesterol (LDL-C)

LDL-C was calculated indirectly using the Friedewald equation [13]:

$$LDL{-}C = TC - (HDL{-}C + TG/5)$$

where TC = total cholesterol and TG = triglycerides.

2.3.6 Determination of Very Low-Density Lipoprotein Cholesterol (VLDL-C)

VLDL-C was estimated according to the formula of Gentile et al. [14]:

$$VLDL{-}C(mmol/L) = TG/2.2$$

2.4 Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). One-way analysis of variance (ANOVA) was applied, followed by Tukey's post-hoc multiple comparison test to assess differences between groups. A p-value < 0.05 was considered statistically significant. Graphs were generated using the same statistical package.

2.5 Ethical Approval

All experimental procedures were conducted in compliance with national and institutional guidelines for the use of laboratory animals. Ethical clearance was obtained from the Rivers State University Ethical Committee.

3.0 RESULTS

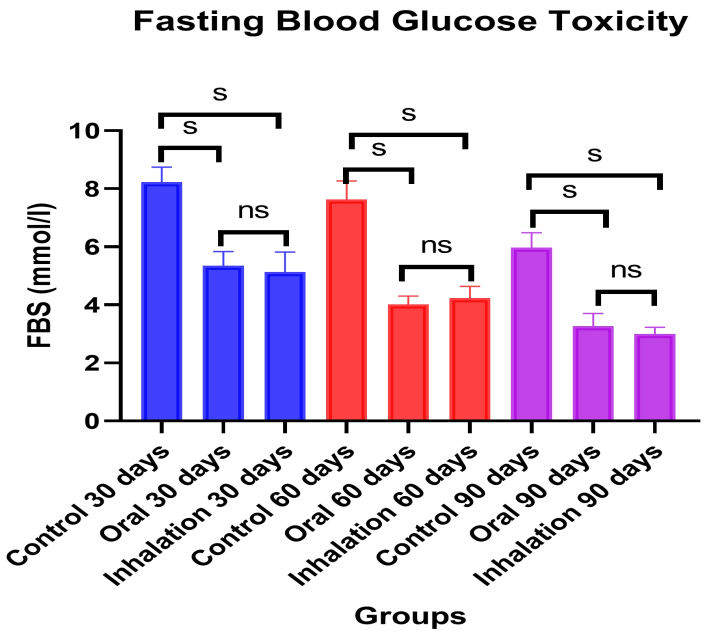

Figure 3.1: Mean ± SD Analysis of FBG parameter in the serum of rabbits treated with dichlorvos by inhalation exposure.

Fig 3.1 shows that at 30 days, there was a significant reduction ($p < 0.05$) in fasting glucose level in the exposed groups at 30 days, 60 days and 90 days compared to corresponding control groups. However, there was no sigificant reduction difference ($p > 0.05$)between the exposed groups.

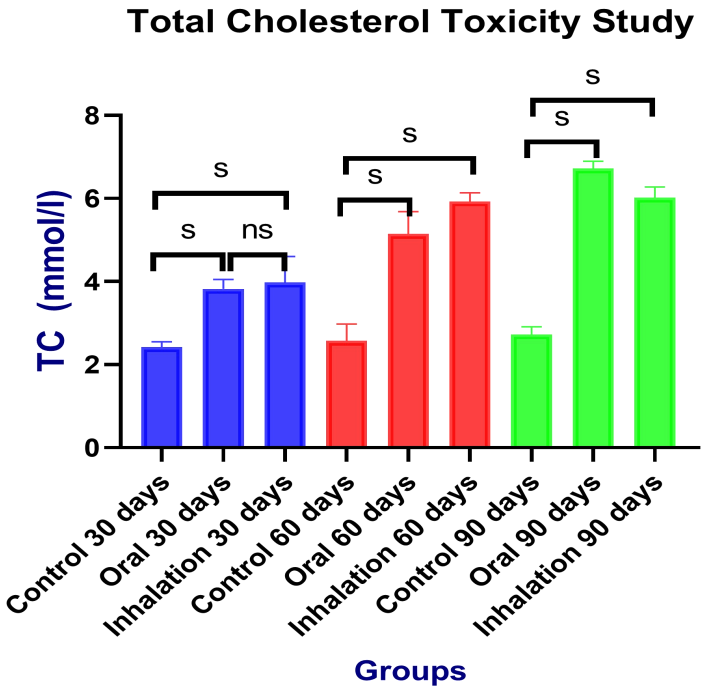

Figure 3.2: Mean ± SD Analysis of Total Cholesterol Toxicity parameter in the serum of rabbits treated with dichlorvos by inhalation exposure.

At 30 days, both oral and inhalation groups exhibited significant increases in cholesterol compared with controls ($p < 0.05$). At 60 days, both oral and inhalation groups exhibited significant increases in cholesterol compared with controls ($p < 0.05$). At 90 days, a marked elevation was observed in both exposure routes ($p < 0.01$), with oral exposure producing higher values.

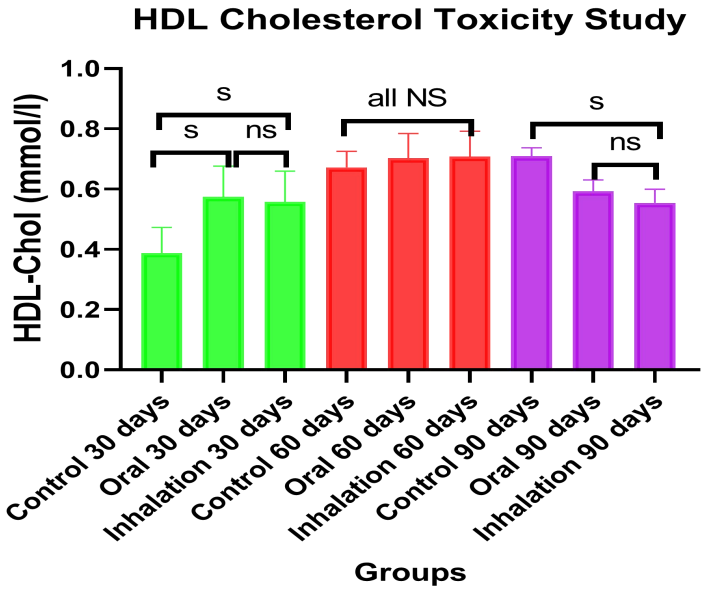

Figure 3.3: Mean ± SD Analysis of HDL Cholesterol parameters in the serum of rabbits treated with dichlorvos by inhalation exposure.

HDL-C, a cardioprotective marker, showed significant changes in Fig 3.3. At 30 days, there was a significant increase in the exposed group compared to the control. By 60 days, HDL-C level had no significant difference aross the groups. At 90 days, HDL-C levels were markedly decreased ($p < 0.001$), with inhalation exposure producing the lowest values.

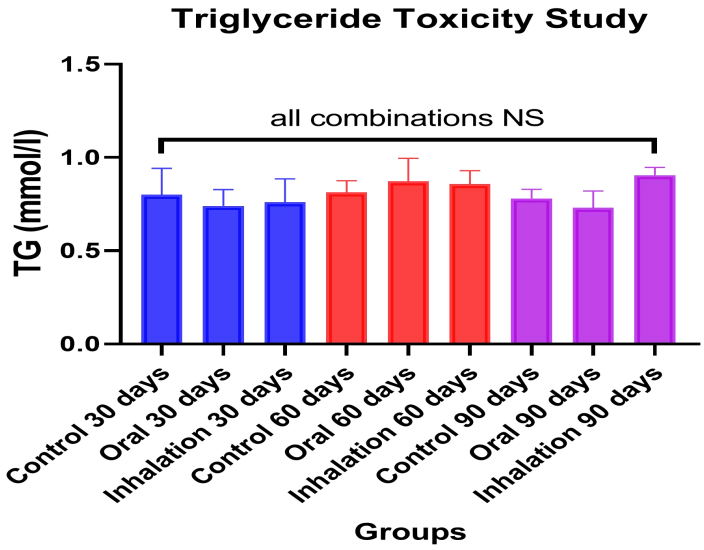

Figure 3.4: Mean ± SD Analysis of Triglyceride parameters in the serum of rabbits treated with dichlorvos by inhalation exposure.

Fig 3.4 showed that serum triglycerides remained comparable among groups at all time points (30 days, 60 days and 90 days).

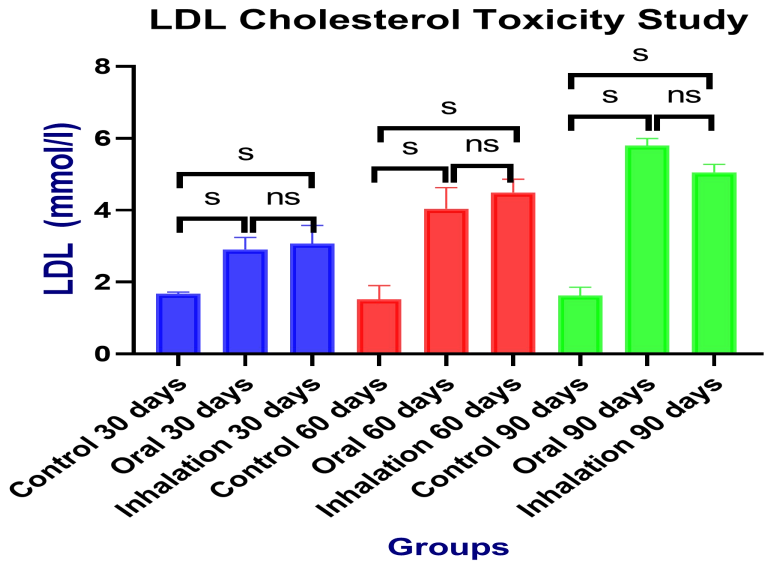

Figure 3.5: Mean ± SD Analysis of LDL Cholesterol parameter in the serum of rabbits treated with dichlorvos by inhalation exposure

Fig 3.5 showed that LDL-C levels was significantly increased in the exposed groups after 30 days. Similarly, at 60 days, both oral and inhalation exposure groups showed significant increases compared with controls ($p < 0.05$). By 90 days, LDL-C was markedly elevated in exposed groups ($p < 0.001$).

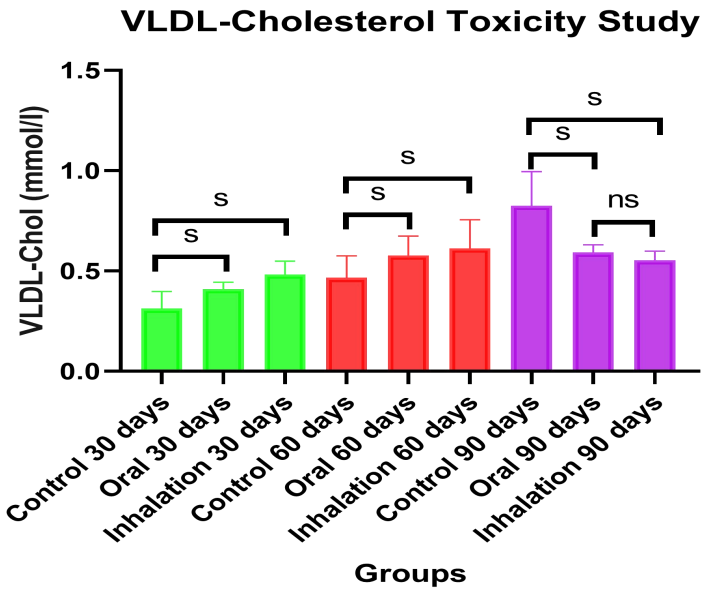

Figure 3.6: Mean ± SD Analysis of VLDL-Cholesterol parameter in the serum of rabbits treated with dichlorvos by inhalation exposure

In Fig 3.6, VLDL-C levels significantly increased at 30 days in both oral and inhalation exposed groups. Similarly, VLDL-C levels significantly increased at 60 days in both oral and inhalation exposed groups. However, VLDL-C levels significantly decreased at 90 days in both oral and inhalation exposed groups.

DISCUSSION

The present study investigated the effects of chronic dichlorvos exposure on serum glucose and lipid parameters in rabbits, with a focus on understanding its metabolic and cardiovascular implications. Our findings demonstrated significant alterations in fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C), while serum triglycerides remained largely unaffected. These observations indicate that dichlorvos exposure induces both hypoglycemic and dyslipidemic effects, which may predispose to metabolic imbalance and cardiovascular risk.

The significant reduction in FBG observed at all time points in exposed groups suggests that dichlorvos interferes with glucose regulation, consistent with earlier reports linking organophosphate pesticides to hypoglycemia. This reduction may be due to impaired gluconeogenesis and glycogenolysis arising from pesticide-induced hepatotoxicity, as previously reported by Gourdarz et al. [6]. Moreover, inhibition of acetylcholinesterase by dichlorvos could enhance peripheral glucose utilization through increased parasympathetic stimulation, further contributing to lowered circulating glucose levels [4]. Persistent hypoglycemia, as observed in this study, is a potential indicator of hepatocellular injury and impaired energy homeostasis.

Total cholesterol levels increased significantly across all durations of exposure, with oral administration showing stronger effects than inhalation at 90 days. Elevated serum cholesterol is an important predictor of atherogenesis and cardiovascular disease [8]. The rise in cholesterol may reflect dichlorvos-induced hepatic dysfunction, resulting in altered lipoprotein synthesis and metabolism. Similar findings were reported by Arthur et al. [3], who observed significant lipid disturbances in dichlorvos-exposed animals. The increase in LDL-C and VLDL-C further supports this dyslipidemic trend, suggesting that dichlorvos promotes the accumulation of atherogenic lipoproteins.

Interestingly, HDL-C, a cardioprotective lipoprotein, exhibited a biphasic response. At 30 days, HDL-C levels were elevated in exposed groups, which may represent an early adaptive response to oxidative stress and lipid imbalance. However, by 90 days, HDL-C was markedly reduced, especially in the inhalation group. This decline is of particular concern, as reduced HDL-C has been strongly associated with impaired reverse cholesterol transport and increased risk of atherosclerosis [9]. The temporal shift from initial increase to later depletion highlights the progressive metabolic toxicity of dichlorvos with prolonged exposure.

Triglyceride levels remained relatively unchanged throughout the study. This finding contrasts with some earlier studies that reported significant elevations in triglycerides following organophosphate exposure [5]. The lack of marked change here could be due to species-specific differences in lipid handling or the sublethal dose employed. Nonetheless, the significant rise in VLDL-C, particularly at 30 and 60 days, indicates that dichlorvos still affects triglyceride transport and distribution. The subsequent decline in VLDL-C at 90 days may be attributed to advanced hepatic impairment, limiting lipoprotein synthesis.

Taken together, these findings demonstrate that dichlorvos exerts complex metabolic effects characterized by sustained hypoglycemia, persistent hypercholesterolemia, progressive LDL-C elevation, and late-onset HDL-C depletion. Such alterations significantly tilt the balance towards a pro-atherogenic profile, thereby increasing the risk of cardiovascular complications. Moreover, the observation that oral administration

produced stronger effects than inhalation at later time points underscores the importance of exposure route in determining toxic outcomes.

From a public health perspective, these results are alarming given the widespread and often indiscriminate use of dichlorvos in Nigeria and other developing countries. Chronic exposure, whether occupational, environmental, or domestic, may contribute silently to the burden of metabolic disorders and cardiovascular disease. This underscores the urgent need for stricter regulation, improved awareness, and safer alternatives to dichlorvos

Conclusion

This study demonstrates that chronic dichlorvos exposure induces significant alterations in glucose and lipid metabolism in rabbits, characterized by sustained hypoglycemia, progressive hypercholesterolemia, increased LDL-C and VLDL-C, and late-onset reduction in HDL-C. These changes collectively favor a pro-atherogenic profile, thereby increasing the risk of cardiovascular complications. The findings highlight the potential public health risks associated with prolonged dichlorvos exposure and underscore the need for regulatory control and safer pesticide alternatives.

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