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Comparative Effect of Withdrawal from Exposure on Gasoline and Diesel Induced Nephrotoxicity in Male Albino Wistar Rats

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Abstract

Exposure to gasoline and diesel has been reported to induce nephrotoxicity in rats. This study was designed to assess the effect of withdrawal from exposure on the nephrotoxic effects associated with oral exposure to gasoline and diesel in male rats. Four groups of the experimental test rats were respectively exposed orally to diesel and gasoline solvents (4.0 mg/kg/day, 6 days/week) for 60 days, after which two respective groups were sacrificed for nephrotoxicity assay while the remaining two groups were withdrawn from exposure for the next 60 days before sacrificing them for biochemical assay. The results showed that oral exposure to diesel and gasoline induced a significant ($p<0.05$) increase in serum creatinine, urea, blood urea nitrogen (BUN) and kidney tissue malondialdehyde (MDA), as well as decrease in kidney tissue reduced glutathione (GSH) concentrations in rats. However, the percentage increase in serum creatinine, urea, BUN, kidney tissue MDA, and decrease in kidney tissue GSH concentrations recorded for rats exposed to diesel (300.1 ± 30.8, 130.3 ± 18.5, 125.6 ± 16.4, 141.8 ± 10.4 and 75.0 ± 8.6 percents, respectively) were significantly higher ($p<0.05$) compared to the percentages recorded for rats exposed to gasoline (150.0 ± 17.5, 80.3 ± 13.2, 72.1 ± 11.4, 120.9 ± 15.2 and 61.5 ± 10.1 percents, respectively). The result of this study also showed that withdrawal from exposure reverses the levels of serum creatinine, urea, BUN, and kidney tissue MDA and GSH to the levels approximately within the control range. This study confirms that oral exposure to diesel and gasoline may be a risk factor for nephrotoxicity, with diesel being more nephrotoxic than gasoline, and that withdrawal from exposure for equal duration of the exposure period is capable of reversing the induced nephrotoxicity in rats.

Keywords: Gasoline; Diesel; Nephrotoxicity; Withdrawal from exposure; Reversal of nephrotoxicity

Introduction

Petroleum, either in its crude or refined form, is one of the most widely utilized natural resources in most oil-producing economy. It forms the mainstay of the economy and the major determinant of national finance and industry in such Societies. The oil exploration, production and utilization activities have brought with them an alarming increase in industrial activities, which have contributed immensely to the unnecessary disruption of the natural ecological setting of the oil producing areas. The intensity of these consequences on different species of organisms varies with the quantity and fractions of the petroleum products released into the different environment [1-7]. It is generally known that the normal physiological condition of an organism may be altered by a number of environmental factors. These factors are present in the environment either in gaseous, liquid, semi-solid, or solid states. They may gain access into the organisms through inhalation, ingestion or dermal contact. Petroleum hydrocarbons are among the chemical substances that are ubiquitous in the environment. Exposure to these petroleum hydrocarbons could be from gasoline and/or diesel fumes at the pumps, accidental or intentional ingestion of the liquid solvent.

Diesel and gasoline fuels are mixtures of hydrocarbons. Particularly, diesel fuel is made of chemical composition of 12-20 carbon atoms per molecule, and approximately 30% n-paraffin, 45% cycloalkanes and 25% aromatics [8]. It is also known that the constituent of petroleum products and their toxicity effects reflects the properties of the crude oil from which they are distilled [9,10]. Generally, petroleum hydrocarbons, including those from diesel and gasoline fuel have been reported to be nephrotoxic, and could cause acute renal failure [3,4,11]. The toxicological effect of any substance may be explained as an interference with the cellular or subcellular process, which leads to a disruption of the normal metabolism of a living organism upon exposure to such substance. It has been reported that petroleum hydrocarbon magnified their toxic effects by competing with some endogenous metabolites or block some pathways, this interference may or may not be lethal [1,2,5-7,12]. The toxic effects of petroleum hydrocarbon are exerted on variety of organs of living systems such as the lungs, liver and kidney [13]. It has also been documented that exposure of rat to gasoline exhaust and organic extracts of the exhaust particulate caused a dose- and time- dependent increase in oxygenases and glutathione-s-transferase in the liver, kidney and lung microsomes; as well as pulmonary dysfunction and parenchymal damage among dogs [14]. Other adverse effects associated with exposure to petroleum vapours have been reported in both the experimental animals and humans [15-21].

Like other known xenobiotics, the chemical pollutants from gasoline vapours may be metabolically transformed into various metabolites in the body [17]. Some of these metabolites may be very reactive, interacting in various ways with the metabolizing, transporting and excreting tissues to elicit toxic effects [22]. The interaction of these metabolites with the renal tissues may cause cellular injury,

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Group	No. of rats	Treatment
1a	6	Administered with 0.5 ml of distilled water for 60 days
1b	6	Withdrawn from distilled water administration for the next 60 days
2a	6	Administered with 0.5 ml of vegetable oil for 60 days
2b	6	Withdrawn from vegetable oil administration for the next 60 days
3a	6	Administered with 4.0 mg/kg body weight of gasoline fuel for 60 days
3b	6	Withdrawn from 4.0 mg/kg body weight of gasoline fuel administration for the next 60 days
4a	6	Administered with 4.0 mg/kg body weight of diesel fuel for 60 days
4b	6	Withdrawn from 4.0 mg/kg body weight of diesel fuel administration for the next 60 days

Table 1: Distribution and treatment of experimental animals in the respective groups.

hence, damage to the tissues. Once the renal tissues are damaged, the overall functionality of the kidneys may be compromised. The kidney functions may be assessed from the level of some electrolytes (such as K+, Na+, Cl-) and metabolites (such as creatinine, urea and blood urea nitrogen) in the plasma [23-25]. Generally, tissue damage resulting from lipid peroxidation free radical generation may also be monitored from the tissue malondialdehyde (MDA) and glutathione (GSH) levels [26,27]. Renal dysfunction may therefore be caused by several diseased conditions and exposure to certain reactive or toxic metabolites [25,28,29]. Exposure to diesel and gasoline fuel has been reported to induce nephrotoxicity in experimental animals [4]. However, there is paucity of information on whether the gasoline and diesel induced nephrotoxicity may be reversed by withdrawal from exposure. Hence, this work is aimed at assessing the comparative effect of withdrawal from exposure on gasoline and diesel induced nephrotoxicity in male albino Wistar rats.

Materials and Methods

Animal handling and treatment

Forty eight apparently normal matured male albino Wistar rats, weighing between 180 to 200 g were obtained from Biochemistry Department Experimental Research Animal House of the University of Calabar, Calabar, Nigeria. The animals were allowed one week of acclimatization to laboratory conditions and handling, after which they were distributed, according to weight into eight groups as presented in Table 1. The animals were housed individually in cages with plastic bottom and wire mesh top (North Kent Co. Ltd) and fed with normal rat chow (Guinea Feeds Product) purchased from the High Quality Livestock Feeds stores, Calabar, Nigeria. They were supplied with tap water *ad libitum* throughout the experimental period. The animals were maintained in the animal room adequately ventilated under standard conditions (ambient temperature, 25 ± 2°C, and relative humidity, 46%, with a light/dark cycle of 12/12h).

The gasoline and diesel fuel were respectively solubilized in Grand pure soya oil (cholesterol-free vegetable oil), as a vehicle before administering to the animals in the respective groups. All administrations were carried out orally using orogastric tube. The test doses of the chemical substances used in this study (gasoline and diesel fuels) were determined from the LD50/acute toxicity study. The Grand pure soya oil used in this study was obtained from Grand Cereals & Oil Mills Ltd, Jos, Nigeria, while gasoline and diesel fuel were obtained from obtained from the Nigerian National Petroleum Corporation (NNPC) Mega Station along Mutala Muhamed Highway, Calabar, Nigeria.. The study was carried out according to the Guidelines of the Institution's Animal Research Ethics Committee, and in accordance with the Guide for the Care and Use of Laboratory Animals [30].

Collection and preparation of blood and kidney tissues for analyses

Blood samples were obtained from rats by cardiac puncture, under chloroform vapour anesthesia, after 48 hours of termination of administration into sterile plain screw-cap sample bottles. The blood samples were allowed to clot and then centrifuged with Table-top centrifuge (MSE model, England) at 3000 rpm for 10 minutes to obtain the serum, which was subsequently used for the biochemical assay. The sera separated were preserved in a refrigerator and analysed within 48 hours of separation. The kidney tissues were also collected and immediately perfused with 60 to 100 of ice cold 0.9% NaCl solution for estimation of MDA and reduced GSH.

Biochemical analyses

Biochemical analyses carried out included measurement of serum creatinine and urea concentrations. Serum urea was estimated by the end point colorimetric method using Dialab reagent kits [31]. In this method, urease enzyme hydrolyses urea to ammonia and carbon dioxide. The ammonia so formed reacts with alkaline hypochloride and sodium salicylate in the presence of sodium nitroprusside to form a coloured chromophore whose absorbance was measured with DREL 3000 HACH (England) model spectrophotometer. Blood urea nitrogen level was derived from serum urea [31]. The concentration of serum creatinine was assayed based on the reaction of creatinine with an alkaline solution of sodium picrate to form a red complex [32].

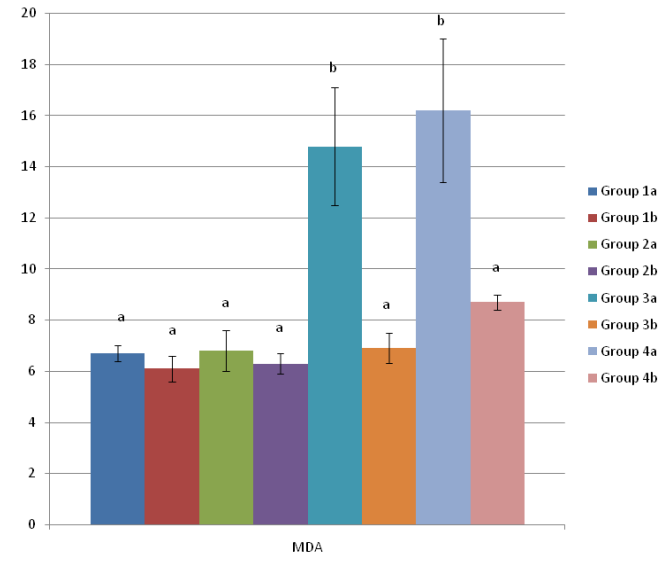

Figure 1: Kidney tissue MDA (%TBARS) levels in the Control rats orally gavaged with 0.5 ml saline water for 60 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml saline water for 60 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 60 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 60 days (Group 2b), Test rats orally gavaged with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3a), Test rats withdrawn from oral gavage with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3b), Test rats orally gavaged with 4.0mg/kg bw of diesel fuel for 60 days (Group 4a) and Test rats withdrawn from oral gavage with 4.0mg/kg bw of diesel for 60 days (Group 4b) . Each value represents mean ± SEM; n = 6; bP≤ 0.05 compared to a.

The red colored complex which is proportional to the concentration of creatinine in the sample was measured spectrophotometrically. Kidney tissues MDA and reduced GSH were analyzed according to the methods described by Wallin et al. [33] and (King and Wootton, [34], respectively. All absorbance readings were taken with DREL3000 HACH model spectrophotometer.

Statistical analysis

Results obtained were presented as mean ± S.E.M and statistically analysed using one-way analysis of variance (ANOVA), using SPSS window statistical software programme. Student "t" test was used for pair-wise significance, and differences were considered significant at $p<0.05$ according to Artimage and Berry [35].

Results

The results of this study are presented in Figures 1-6. The results of this study showed that oral exposure of rats to gasoline and diesel fuel caused a significant ($p<0.05$) increase in kidney tissue MDA level (Figure 1), decrease in kidney tissue GSH level (Figure 2), increase in serum creatinine (Figure 3), urea (Figure 4) and Blood urea nitrogen (BUN) concentrations (Figure 5), compared to the respective levels recorded for rats in the control groups.

However, it was observed that the percentage increase in kidney tissue MDA, decrease in kidney tissue GSH, increase in serum creatinine, urea and BUN concentrations recorded for rats exposed to diesel fuel were significantly ($p<0.05$) higher than the percentage increase in kidney tissue MDA, decrease in kidney tissue GSH, increase in serum creatinine, urea and BUN concentrations recorded for rats exposed to gasoline fuel (Figure 6). This observation indicated that oral exposure to gasoline and diesel fuel is a risk factor for nephrotoxicity induction, and that the nephrotoxicity risk associated with exposure to diesel fuel is higher than that associated with exposure to gasoline fuel.

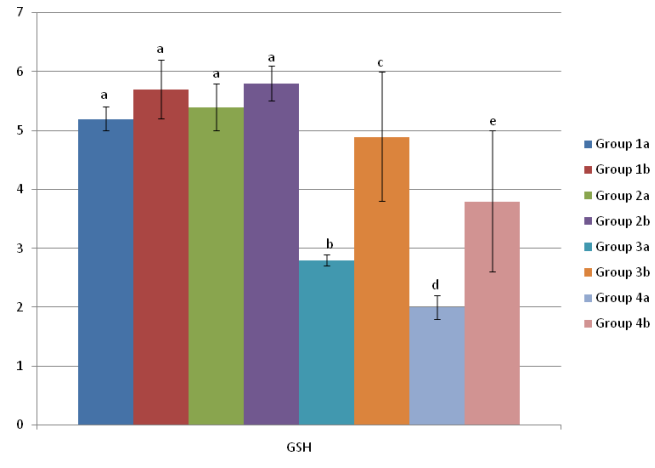

Figure 2: Kidney tissue GSH (mg/g tissue) levels in the Control rats orally gavaged with 0.5ml saline water for 60 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml saline water for 60 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 60 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 60 days (Group 2b), Test rats orally gavaged with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3a), Test rats withdrawn from oral gavage with 4.0mg/kg bw of gasoline fuel for 60 days (Group 3b), Test rats orally gavaged with 4.0 mg/kg bw of diesel fuel for 60 days (Group 4a) and Test rats withdrawn from oral gavage with 4.0 mg/kg bw of diesel for 60 days (Group 4b) . Each value represents mean ± SEM; n = 6; bP≤ 0.05 compared to a, c, d & e; cP≤ 0.05 compared to e; eP≤ 0.05 compared to a.

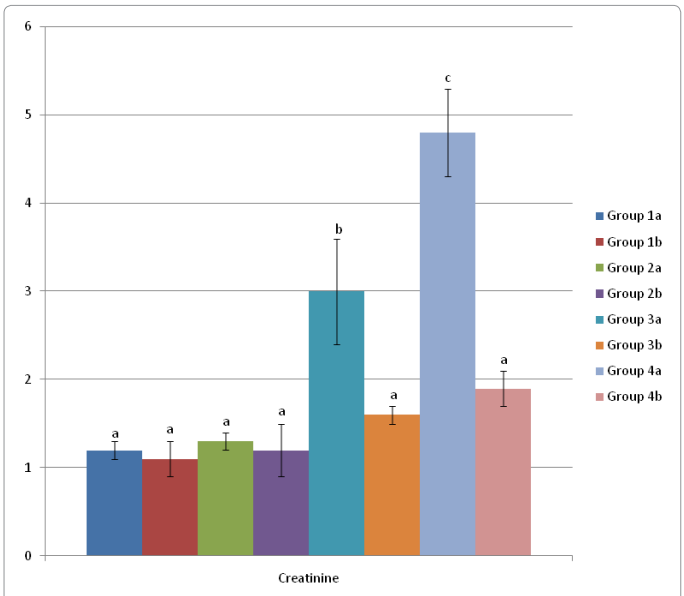

Figure 3: Serum creatinine (mg/dl) levels in the Control rats orally gavaged with 0.5 ml saline water for 60 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml saline water for 60 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 60 days (Group 2a), Control rats withdrawn from oral gavage with 0.5ml of vegetable oil for 60 days (Group 2b), Test rats orally gavaged with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3a), Test rats withdrawn from oral gavage with 4.0 mg/kg bw of gasoline fuel f or 60 days (Group 3b), Test rats orally gavaged with 4.0 mg/kg bw of diesel fuel for 60 days (Group 4a) and Test rats withdrawn from oral gavage with 4.0mg/kg bw of diesel for 60 days (Group 4b). Each value represents mean ± SEM; n = 6; bP≤ 0.05 compared to a & c; cP≤ 0.05 compared to a.

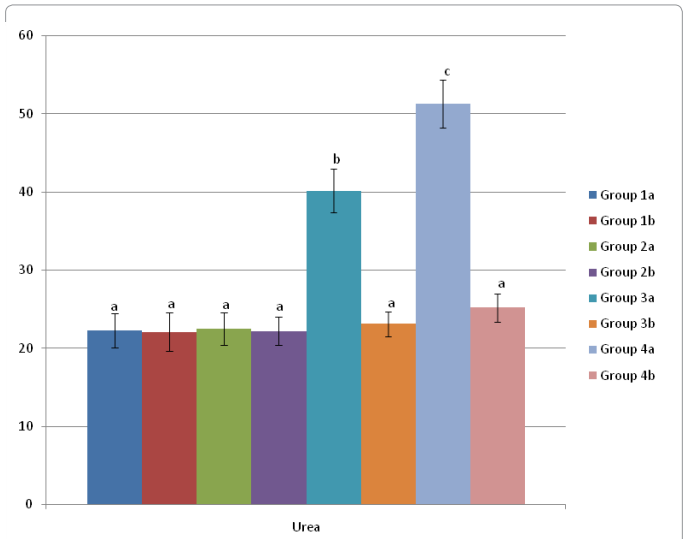

Figure 4: Serum Urea (mg/dl) levels in the Control rats orally gavaged with 0.5 ml saline water for 60 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml saline water for 60 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 60 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 60 days (Group 2b), Test rats orally gavaged with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3a), Test rats withdrawn from oral gavage with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3b), Test rats orally gavaged with 4.0 mg/kg bw of diesel fuel for 60 days (Group 4a) and Test rats withdrawn from oral gavage with 4.0 mg/kg bw of diesel for 60 days (Group 4b). Each value represents mean ± SEM; n = 6; bP≤ 0.05 compared to a & c; cP≤ 0.05 compared to a.

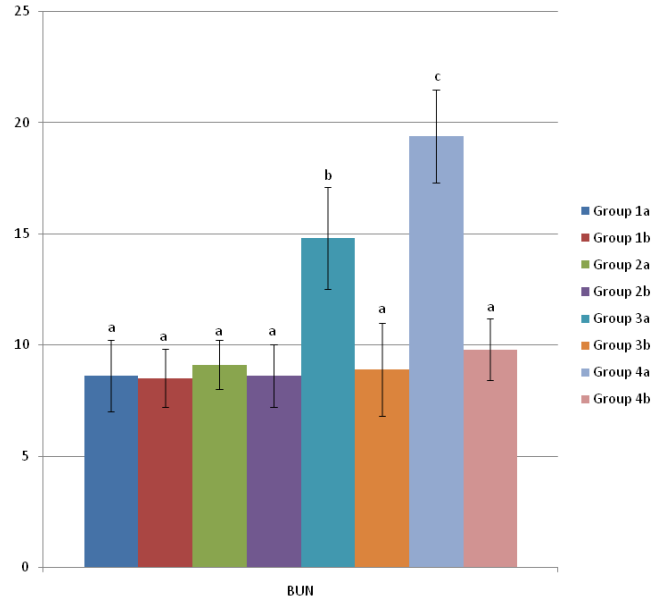

Figure 5: Serum BUN (mg/dl) levels in the Control rats orally gavaged with 0.5ml saline water for 60 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml saline water for 60 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 60 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 60 days (Group 2b), Test rats orally gavaged with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3a), Test rats withdrawn from oral gavage with 4.0 mg/kg bw of gasoline fuel for 60 days (Group 3b), Test rats orally gavaged with 4.0 mg/kg bw of diesel fuel for 60 days (Group 4a) and Test rats withdrawn from oral gavage with 4.0 mg/kg bw of diesel for 60 days (Group 4b). Each value represents mean ± SEM; n = 6; bP≤ 0.05 compared to a & c; cP≤ 0.05 compared to a.

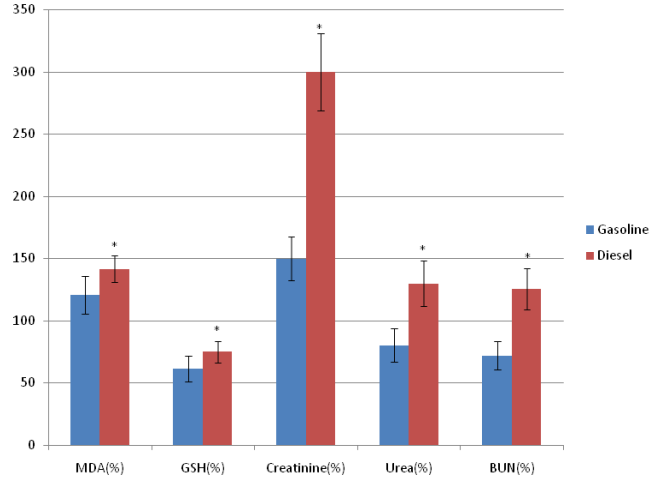

Figure 6: Percentage decrease in kidney tissue MDA, SOD, increase in serum creatinine, urea, and BUN recorded for rats exposed to gasoline and diesel fuel.

It was also observed from the results of this study withdrawal from exposure reversed the elevated kidney tissue MDA, decreased kidney tissue GSH, and raised serum creatinine, urea and BUN concentrations to levels approximately within the control range (Figures 1-5). The reversal of the gasoline and diesel fuel induced alterations in the level of these biochemical indices to near normal control range, suggests that the nephrotoxicity effect associated with exposure to gasoline and diesel fuel is reversible.

Discussion

The results of this study show that oral exposure to gasoline and diesel resulted in deterioration of renal function as indicated by significant elevation in serum creatinine, urea and blood urea nitrogen, as well as significant increase in MDA and decrease in GSH concentrations in the kidney tissue of the experimental test rats. However, the increase in serum creatinine, urea and blood urea nitrogen, as well as kidney tissue MDA and GSH recorded in this study was observed to be solvent dependent, with diesel indicating to be higher. These results are consistent with the report of the studies by other researchers on gasoline, kerosene and diesel in rats [3,4,36], and that reported for cisplatin by Miyaji et al. [37] and Behling et al. [26] for experimental animals, and Weiner and Jacobs [38] for human beings. Particularly, exposure to pollutants from such chemical substances as petroleum hydrocarbons, heavy metals and pesticides has been reported to lead to system stress [39]. This present study supports the earlier report by Uboh et al. [3] that diesel vapour tends to contain chemical substance(s) that are more nephrotoxic than gasoline vapour. The specific chemical substituent(s) in diesel and the mechanism (s) responsible for the observed increased nephrotoxicty in rats exposed to diesel is yet to be elucidated. Mortada et al. [40] reported the presence of lead in automobile exhaust as a risk for nephrotoxicity among traffic policemen. While Halder et al. [41] reported that lead is the component of gasoline responsible for nephrotoxicity observed to be associated with exposure to leaded gasoline. Ujowundu et al. [42], also reported that reduced activities of superoxide dismutase and glutathione peroxidase and increase concentration of MDA, indicating hepatic oxidative damage, is associated with diesel petroleum intoxication in rats.

Increased tissue MDA and decreased tissue GSH, recorded in this work, shows that metabolism of the chemical constituents of gasoline and diesel have a resultant lipid peroxidation effect, and lipid peroxidation is one of the known mechanisms of free radical generation in the biological systems. Free radical damage to membrane components of the renal cells may therefore be suggested to be responsible for the nephrotoxic effects recorded in this study, for exposure to gasoline and diesel in rats. The increased MDA and decreased GSH in the renal tissues of the experimental test rats indicates that metabolites of gasoline and diesel constituents may be very reactive, or may be capable of generating free radicals which interact with the membrane macromolecules and cause damage to the renal cells. The role of free radicals in the pathogenesis of the nephrotoxicity has been well documented [26,27]. Also, cisplatin induced production of reactive oxygen species has also been reported by other authors to be implicated in its direct cellular toxicity [43-45]. Hence gasoline and diesel induced free radical production may be suggested to responsible for the oxidative renal damage or nephrotoxicity, reported in this study. This observation is similar to that reported by Srilaxmi et al. [46] and Kalu et al. [47] for the liver tissues of rats administered with CCl4.

The results recorded in this work also reveal that withdrawal from exposure returned elevated serum creatinine, urea BUN, creatinine, renal tissue MDA and decreased GSH concentrations approximately to the normal control levels. However, the percentage reversal of the altered serum creatinine, urea BUN, creatinine, and renal tissue MDA and GSH concentrations recorded for rats exposed to gasoline, following withdrawal from exposure, was moderately higher than those recorded for rats in the group exposed to diesel, though all within the same range as the control. These observations indicate that the nephrotoxic effects associated with oral exposure to gasoline and diesel, within the duration

of the experimental period, may be said to be reversible. The results of this works agree with the report of Cairney [48], that neurological and cognitive impairment from chronic petrol sniffing ameliorates with abstinence and may recover completely, possibly with complete withdrawal from exposure. The reversal of gasoline and diesel induced nephrotoxicity reported in this study also supports the earlier reports of some researchers on the regenerative potential of renal tissues after cellular damage [49-52]. Particularly, Cochrane et al. [51] reported the regenerative potential of the kidney after the established interstitial matrix expansion and medullary ablation associated with unilateral ureteral obstruction in the adult mouse. These researchers reported that GFR in the 6-wk renal-unilateral ureteral obstruction kidneys was restored to 43 to 88% of the GFR in the contralateral unobstructed kidneys.

The moderate differences in percentage reversal of the gasoline and diesel induced nephrotoxicity, following withdrawal from exposure, is not very clear. However, this may be suggested to be attributed to the slight higher nephrotoxic effect recorded for diesel, in comparison to gasoline. In conclusion, the results of this work suggest that exposure to diesel at equal dosage and duration of exposure causes more renal tissue damage than gasoline, that withdrawal from exposure reverses the nephrotoxic effects associated with oral exposure to gasoline and diesel solvents in a solvent dependent pattern, with the rate of reversal of nephrotoxicity induced by gasoline solvent being faster than that caused by diesel.

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