

# Withdrawal from Exposure Reverses Hematotoxicity and Hepatotoxicity Caused by Oral Exposure to Nitrocellulose Thinner in Male Rats

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## Abstract

Nitrocellulose thinner (*nct*) is one of the commonly used industrial chemical solvents. Individuals involved in furniture, paint, automobile manufacture and repairs occupations, and those living around these workplace environments are at the risk of exposure to *nct*'s constituents ubiquitously released into the environment. Oral exposure to this solvent has been reported to cause haematotoxicity and hepatotoxicity in rat model. This study assessed the impact of withdrawal from exposure, on *nct* induced-haematotoxicity and hepatotoxicity in male albino Wistar rats. Four groups, of twelve male rats each, were orally exposed to graded concentrations of *nct* for 28 days. After the 28<sup>th</sup> day of exposure, six rats in each group were sacrificed and blood samples collected for *nct* induced-haematotoxicity and hepatotoxicity analyses. The remaining six rats in each group were withdrawn from exposure for the next 28 days, after which they were sacrificed, blood samples collected and analyzed for any possible recovery effect from exposure-induced haematotoxicity and hepatotoxicity. The results confirmed that exposure of male rats to *nct* for 28 days caused a significant ( $P < 0.05$ ) concentration-dependent increase in haematotoxic and hepatotoxic indices, compared to the control. However, 28 days withdrawal from exposure produced a significant ( $P < 0.05$ ) reduction in the recorded haematotoxic and hepatotoxic indices, compared to the *nct* exposed groups. The results obtained for rats withdrawn from exposure were within the same range as those obtained for the control group, indicating that withdrawal from exposure may reverse the haematotoxic and hepatotoxic effects associated with exposure to *nct* in male rats.

**Keywords:** Nitrocellulose thinner; Hepatotoxicity; Haematotoxicity; Albumin; Serum protein

## Introduction

Nitrocellulose thinner is an industrial solvents commonly used in furniture, paints and automobile spray painting industries. It contains such organic chemical agents, as ethylbenzene or toluene and butyl acetate, which are known to constitute chemical pollutants in different environments. Literature reports that these chemical pollutants have been detected in household and workplace air [1]. Hence, exposure to chemical pollutants of nitrocellulose thinner in indoor and outdoor environments may be common. Particularly, occupational exposures to mixtures of toluene, ethylbenzene and butyl acetate have been reported in workplaces involving painting or lacquering [2,3]. Exposure to organic solvents generated chemical pollutants may occur through different routes, including inhalation, oral ingestion, or topical route. Although inhalation seems to be the most likely route of exposure to chemical pollutants from volatile solvents, direct and indirect oral ingestion are also possible. In the course of usage, nitrocellulose thinner's constituents are also known to fall out and accumulate in the food and drinks within and around the environments where the solvent is used. Consumption of these contaminated food and drinks by humans and animals forms the basis of oral exposure to this solvent by certain individuals. This therefore justifies our choice of oral route of exposure in this study.

Exposure to different organic solvents has been reported to cause adverse effects on the functional integrity of different tissues in the biological systems [4-11]. However, the role of the liver tissues in the metabolism of foreign organic chemical substances makes it the primarily target tissues to be adversely affected by either the parent compounds, or their metabolites. Literature reports that exposures to various chemical agents express varying adverse effects on the functional integrity of the liver tissues [12,13]. Among the chemical agents reported to be hepatotoxic include such industrial solvents as carbon tetrachloride, toluene, ethylbenzene, butyl acetate, organophosphates

and organochlorides [3,12-14].

Hepatic damage is associated with distortion of these metabolic functions. The activities of such serum liver enzymes as ALT, AST, and ALP, and serum conjugated and total bilirubin, albumin and total proteins are among the biochemical indices commonly used in the assessment of the functional integrity of the liver cells [4,6,7,15-18].

Also, exposure to such organic solvents as gasoline, nitrocellulose thinner, phenylhydrazine, have been reported to cause haematotoxicity, hence anaemic condition [8,19-21]. Typically, it has been reported that sub chronic intoxication of rats with 10 mg of phenylhydrazine per kg body weight per day for 8 days resulted in a marked haemolytic anaemia characterized by decreased red blood cell counts, haemoglobin and packed cell volume [22]. Also, further studies by Jain and Subhramanyam (1978) [23] suggested that phenylhydrazine induces anemia as a consequence of peroxidation of RBC membrane lipids, an effect which may be a result of the auto-oxidation of the drug and the interaction of oxygen radicals with membrane lipids. This study aimed at assessing whether withdrawal from exposure to nitrocellulose thinner reverses the oral exposure-induced haematotoxicity and hepatotoxicity in male albino Wistar rat model.

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## 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. They were fed with standard laboratory diet and tap water. The work was carried out under 12 hours light/dark cycle illumination and room temperature of  $25 \pm 2^\circ\text{C}$ . The animals were divided into eight groups as shown in Table 1 below:

Our preliminary routine laboratory acute toxicity study in mice, gave 40 mg/kg body weight of nitrocellulose thinner (solubilized in Grand pure soya oil) as the  $\text{LD}_{50}$ . Hence, the animals in Groups 3a and b and 4a and b were orally exposed to 20 and 30 mg/kg body weight, respectively, of nitrocellulose thinner for 28 days. The animals in groups 1a, 2a, 3a and 4a were sacrificed, 24 hours after the 28th day of exposure, while animals in groups 1b, 2b, 3b and 4b were withdrawn from exposure for the next 28 days and sacrificed on the 57<sup>th</sup> day of the experimental period.

The nitrocellulose thinner was solubilized in Grand pure soya oil (cholesterol-free vegetable oil), as a vehicle before administering to the animals. The animals in groups 1a and b, and 2a and b were given equal volumes of distilled water, and the vegetable oil, respectively, as the volume used for the nitrocellulose thinner administration vehicle. The Grand pure soya oil was obtained from Grand Cereals and Oil Mills Ltd, Jos, 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 [24].

Collection and preparation of blood and liver tissues for analyses: Blood samples were obtained from rats by cardiac puncture, under chloroform vapour anaesthesia, after 48 hours of termination of nitrocellulose thinner administration into sterile plain screw-cap sample bottles (for biochemical indices) and EDTA-treated screw-cap sample bottles (for haematological indices). The blood samples collected for biochemical indices assay 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 blood samples obtained for haematological assay were analysed within 24 hours of blood collection, while the sera separated for biochemical assay were preserved in a refrigerator and analysed within 48 hours of serum separation. Liver tissues were also collected and immediately perfused with 60 to 100 of ice cold 0.9% NaCl solution for estimation of superoxide dismutase (SOD), glutathione peroxidase (GPX) and malondialdehyde (MDA).

Group	No. of rats	Treatment
1a	6	0.5 ml of distilled water for 28 days
1b	6	Withdrawn from distilled water treatment for 28 days
2a	6	0.5 ml of vegetable oil for 28 days
2b	6	Withdrawn from vegetable oil treatment for 28 days
3a	6	20 mg/kg body weight of nct for 28 days
3b	6	Withdrawn from 20 mg/kg body weight of nct treatment for 28 days
4a	6	30 mg/kg body weight of nct for 28 days
4b	6	Withdrawn from 30 mg/kg body weight of nct treatment for 28 days

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

### Biochemical analyses

Biochemical analyses carried out included measurement of the activities of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), as well as the levels of albumin and total protein. Determination of the activities and concentrations of these biochemical parameters were done by spectrophotometric determination of their absorbances, using analytical grade laboratory reagent kits. The laboratory reagent kits from Biosystems Laboratories (S. A. Costa Brava, Barcelona, Spain) were used to assess the activities of ALT, AST and ALP in the serum. While reagent kits from Randox Laboratories (United Kingdom) were used to assess the activity of GGT, as well as the concentrations of albumin and total protein in the serum. Liver tissues superoxide dismutase (SOD), glutathione peroxidase (GPx) and malondialdehyde (MDA) were analysed according to the methods described by Beuchamp and Fridovich [25], Weiss *et al.* [26], Ellman [27], and Uchiyama and Mihara [28], respectively. All absorbance readings were taken with DREL3000 HACH model spectrophotometer.

### Haematological analyses

The haematological parameters; packed cell volume (PCV), haemoglobin (Hb) concentration, total erythrocyte or red blood cell counts (RBC), total and differential white blood cell counts (WBC); were determined by using the method described by Dacie and Lewis [29].

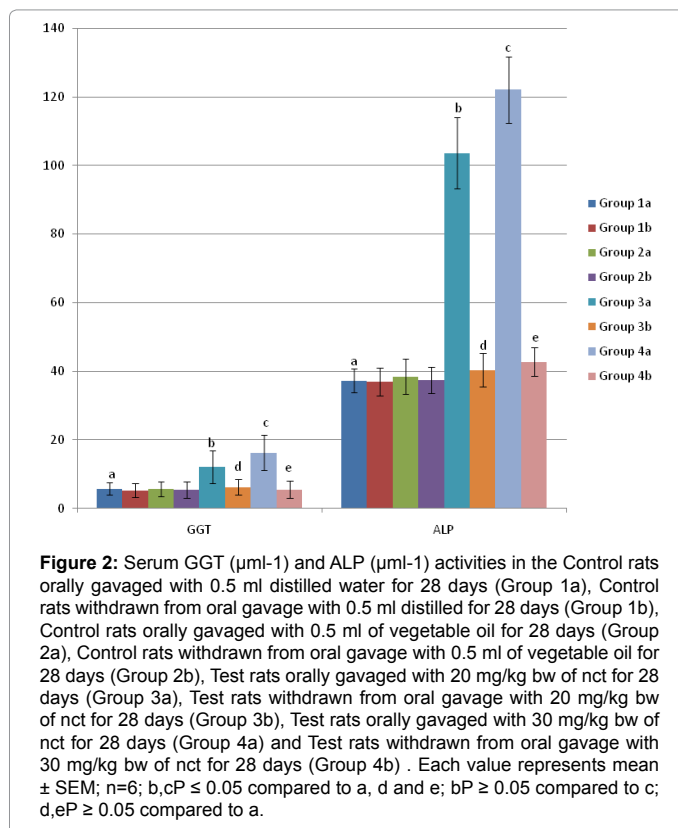
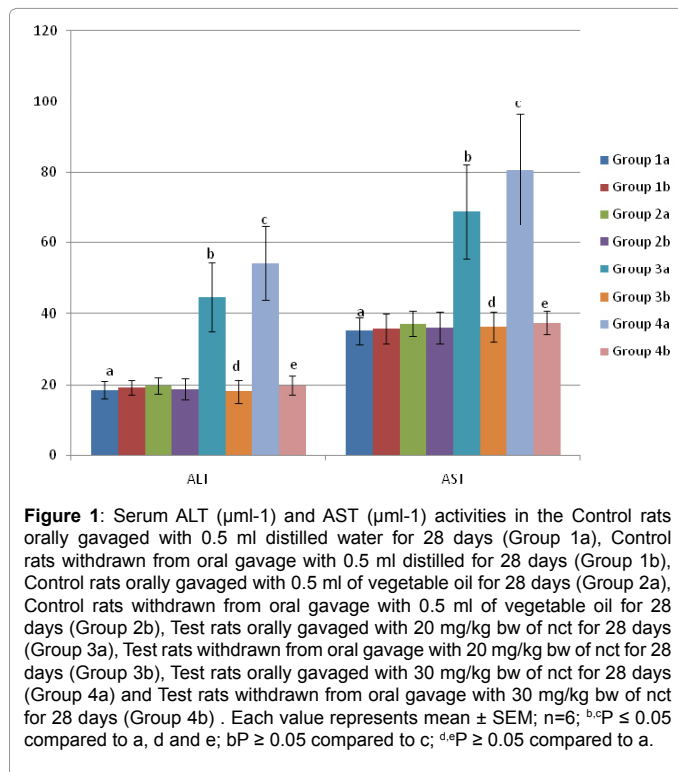
### Statistical analysis

Results obtained were presented as mean  $\pm$  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 [30].

### Results

The results of this study are presented in Figures 1-9. As shown in Figures 1 and 2, oral exposure to nitrocellulose thinner (Groups 3a and 4a) caused a significant ( $p < 0.05$ ) increase in serum ALT, AST, GGT and ALP activities in a dose-dependent pattern, compared to the activities obtained for the control rats given distilled water and vegetable oil (Groups 1a and b and 2a and b). Serum albumin and total protein levels recorded for rats in the experimental test groups, 3a and 4a, were significantly ( $p < 0.05$ ) decreased in dose-dependent pattern compared to the control values (Figure 3). The results of this study also showed that oral exposure to nitrocellulose thinner may induce haematotoxicity. As indicated in Figures 6 and 7, nitrocellulose thinner caused a dose-dependent significant ( $p < 0.05$ ) reduction in red blood cells (RBC), packed cell volume (PCV), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC), compared to the control.

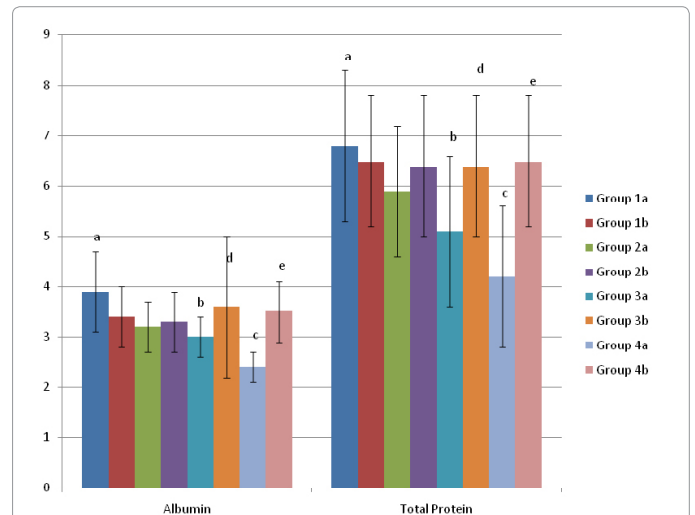
Following the same dose of exposure-dependent pattern as on serum liver enzymes, nitrocellulose thinner caused a significantly ( $p < 0.05$ ) elevated levels of liver tissue MDA, SOD and GPx activities, compared to the activities obtained for rats in the control groups (Figures 4 and 5). However, as shown in Figures 1 and 5, withdrawal from oral exposure to nitrocellulose thinner for the same duration as the exposure period (Groups 3b and 4b), significantly ( $p < 0.05$ ) reversed serum ALT, AST, GGT and ALP activities, albumin and total protein levels, as well as liver tissue MDA, SOD and GPx activities to



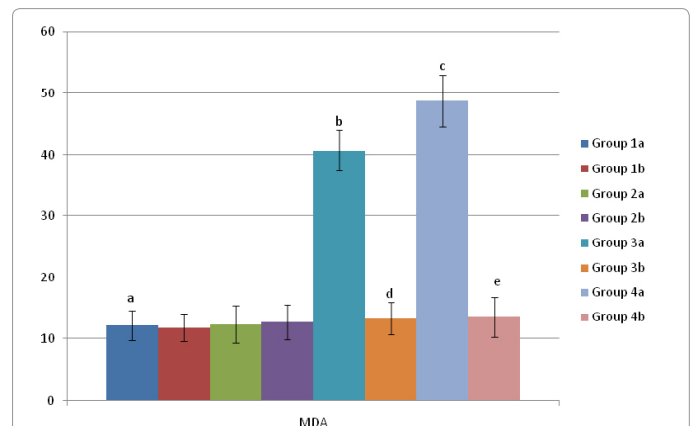
values within the control range. These results indicate that withdrawal from exposure may reverse the harmful effect of nitrocellulose thinner-induced liver injury.

## Discussion

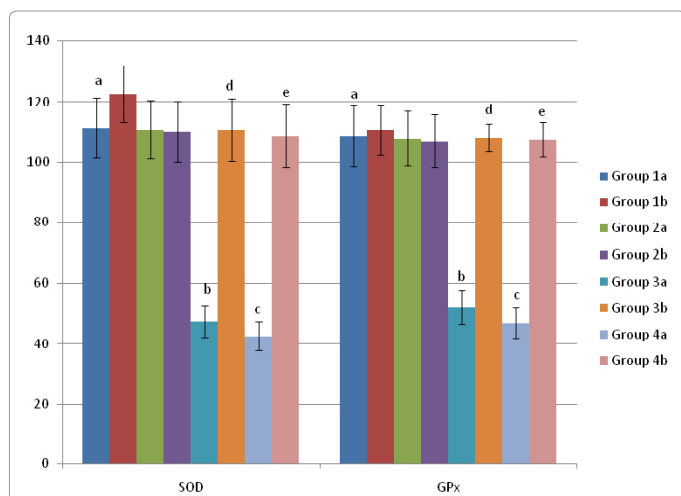
Several chemical agents are known to induce different kinds of toxicities in both humans and experimental animals. Some of these toxic effects are known to be reversible, while others may be irreversible,



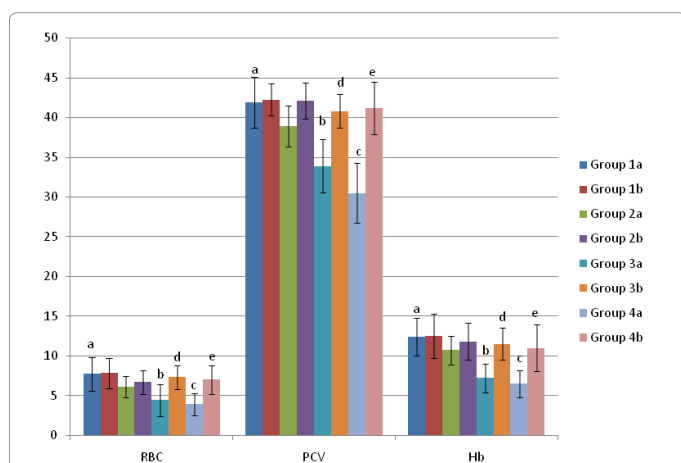
**Figure 3:** Serum albumin and total protein activities in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b). Each value represents mean ± SEM; n=6; <sup>b,c</sup>P ≤ 0.05 compared to a, d and e; <sup>b</sup>P ≥ 0.05 compared to c; <sup>d,e</sup>P ≥ 0.05 compared to a.



**Figure 4:** Liver tissue MDA in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b). Each value represents mean ± SEM; n=6; <sup>b,c</sup>P ≤ 0.05 compared to a, d and e; <sup>b</sup>P ≥ 0.05 compared to c; <sup>d,e</sup>P ≥ 0.05 compared to a.



**Figure 5:** Liver tissue SOD and GPx activities in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled water for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b). Each value represents mean  $\pm$  SEM; n=6; b,cP  $\leq$  0.05 compared to a, d and e; bP  $\geq$  0.05 compared to c; d,eP  $\geq$  0.05 compared to a.



**Figure 6:** Red blood cell (RBC) counts, packed cell volume (PCV) and haemoglobin (Hb) concentration in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled water for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b). Each value represents mean  $\pm$  SEM; n=6; b,cP  $\leq$  0.05 compared to a, d and e; bP  $\geq$  0.05 compared to c; d,eP  $\geq$  0.05 compared to a.

depending on the chemical agents and tissues involved. This study assessed the effect of withdrawal from exposure on the nitrocellulose thinner-induced hepatotoxicity and haematotoxicity in male rats. The results of this study indicated that oral exposure of male rats to nitrocellulose thinner caused significant negative alterations in, tissue

and serum liver function indices, as well as haematological parameters. Particularly, serum ALT, AST, GGT and ALP activities, as well as liver tissue MDA, SOD and GPx activities were observed to be significantly increased, while the values of total protein and total albumin were statistically decreased in all the test animals, following exposure to nitrocellulose thinner. The same adverse effects were also recorded for haematological parameters.

The data presented in this study suggest that the composite constituents of nitrocellulose thinner, or the metabolites of some constituents, exert possible hepatotoxic effect in rat model. This is evidenced by the increased serum ALT, AST, GGT and ALP activities, elevated levels of liver tissue MDA, SOD and GPx activities, as well as decreased serum albumin and total protein levels. The nitrocellulose thinner-induced hepatotoxicity reported in this study agrees with the reports of other researchers on such chemicals as carbon tetrachloride, gasoline, endosulfan [6,7,16,31-33]. The nitrocellulose thinner induced hepatotoxicity reported in this study may be attributed to the oxidative stress caused by the increased lipid peroxidation (increased MDA level) and reduction in SOD and GPx activities, as reported by for carbon tetra chloride and potassium bromate by Abd El-Ghany [32], Waffa and Farida [33]. This observation therefore suggests that the constituents of nitrocellulose thinner, or their metabolites, are reactive and might have interacted with the liver tissues and caused damages to the tissues. In support of the results obtained from this study, high serum ALT levels have also been reported by Lundberg et al. [34] among the painters, who possibly are frequently exposed to nitrocellulose thinner in the course of their occupational activities. The results of this study are also in correlation with the results of the study of Patil et al. [35], on the effect of occupational lead exposure in battery manufacturing workers, silver jewellery workers and spray painters on liver functions.

The results recorded for this study also indicated that exposure to nitrocellulose thinner have adverse effect on the haematological indices, hence haematotoxicity, in rats. The haematotoxicity observed to be associated with oral exposure to nitrocellulose in this study agrees with our earlier reports on nitrocellulose thinner and gasoline [8,19,36], and that of other workers on such chemical agents as phenylhydrazine, cadmium chloride, crude oil, some contraceptives, and pyrethroid insecticide [23,37-40]. Typically, it has been reported that sub chronic intoxication of rats with 10 mg of phenylhydrazine per kg body weight per day for 8 days resulted in a marked haemolytic anaemia characterized by decreased red blood cell counts, haemoglobin and packed cell volume [22]. Also, further studies by Jain and Subhramanyam (2004) suggested that phenylhydrazine induces anemia as a consequence of peroxidation of RBC membrane lipids, an effect which may be a result of the auto-oxidation of the drug and the interaction of oxygen radicals with membrane lipids. Increased liver tissue MDA level, SOD and GPx activities recorded in this study therefore gives a strong indication that the nitrocellulose thinner-induced haematotoxicity reported in this study may be as result of oxidative stress induced haemolytic and suppression of the haematopoietic activities in the experimental subjects.

It also observed from the results of this study that withdrawal from exposure reversed the haematotoxicity and hepatotoxicity observed to be associated with exposure to nitrocellulose thinner. Although the specific mechanism responsible for this reversal effect is not very clear, it has been reported that liver tissues possess the inherent remarkable capacity to regenerate after injury and to adjust its size to match its host [41,42]. According to Michalopoulos and DeFrances [42], hepatic regeneration is triggered by the appearance of circulating mitogenic



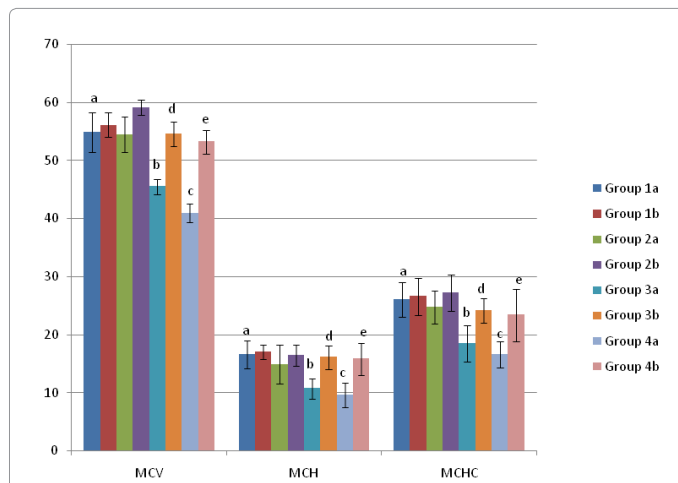


Figure 7: MCV, MCH and MCHC concentration in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b) . Each value represents mean  $\pm$  SEM; n=6; b,cP  $\leq$  0.05 compared to a, d and e; bP  $\geq$  0.05 compared to c; d,eP  $\geq$  0.05 compared to a.

Also, exposure to nitrocellulose thinner resulted in a dose-dependent significant ( $p < 0.05$ ) increase in platelet count, total white blood cell (TWBC), monocytes and neutrophils, compared to the control (Figures 8 and 9). However, these negative alterations, indicating haematotoxic condition, were significantly ( $p < 0.05$ ) reversed following withdrawal from exposure.

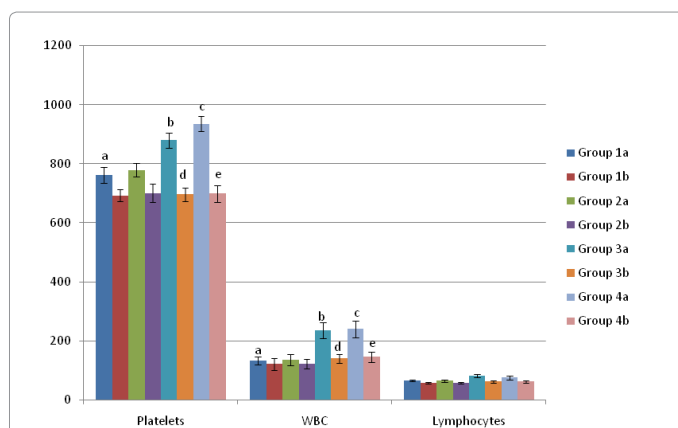


Figure 8: Platelets ( $\times 10^3 \mu\text{L}^{-1}$ ), WBC ( $\times 10^3 \mu\text{L}^{-1}$ ) and Lymphocytes (%) in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b) . Each value represents mean  $\pm$  SEM; n=6; b,cP  $\leq$  0.05 compared to a, d and e; bP  $\geq$  0.05 compared to c; d,eP  $\geq$  0.05 compared to a.

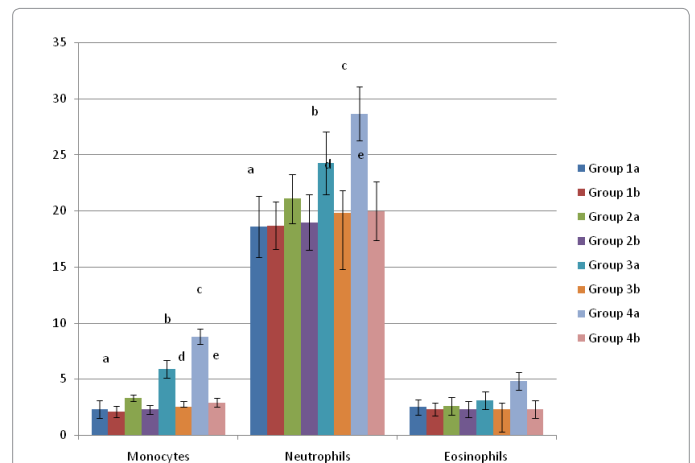


Figure 9: Monocytes (%), Neutrophils (%) and Eosinophils (%) level in the Control rats orally gavaged with 0.5 ml distilled water for 28 days (Group 1a), Control rats withdrawn from oral gavage with 0.5 ml distilled for 28 days (Group 1b), Control rats orally gavaged with 0.5 ml of vegetable oil for 28 days (Group 2a), Control rats withdrawn from oral gavage with 0.5 ml of vegetable oil for 28 days (Group 2b), Test rats orally gavaged with 20 mg/kg bw of nct for 28 days (Group 3a), Test rats withdrawn from oral gavage with 20 mg/kg bw of nct for 28 days (Group 3b), Test rats orally gavaged with 30 mg/kg bw of nct for 28 days (Group 4a) and Test rats withdrawn from oral gavage with 30 mg/kg bw of nct for 28 days (Group 4b) . Each value represents mean  $\pm$  SEM; n=6; b,cP  $\leq$  0.05 compared to a, d and e; bP  $\geq$  0.05 compared to c; d,eP  $\leq$  0.05 compared to a.

factors. As reported by the author, this conclusion was originally supported by experiments demonstrating that quiescent fragments of liver that had been transplanted to extrahepatic sites would begin to proliferate soon after partial hepatectomy, and also that hepatectomy in one of a pair of parabiotic rats led to hepatic proliferation in the other of the pair. The reversal of nitrocellulose thinner induced haematotoxicity and hepatotoxicity, following withdrawal from exposure reported in this study may follow a similar mechanism reported by Michalopoulos and DeFrances [42]; however, it is hereby considered a subject for further studies. In conclusion, the results of this present study showed that withdrawal from exposure reverses the nitrocellulose thinner-induced haematotoxicity and hepatotoxicity in male albino Wistar rat model.

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