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BH Priyadarshi
Veterinary Officer, Livestock Research Station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar, Gujarat, India

DV Joshi
Principal, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

BJ Patel
Professor and Head, Department of Veterinary Pathology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

SH Raval
Assistant Professor, Department of Veterinary Pathology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

HA Patel
Assistant Professor, Polytechnic in Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Corresponding Author:
BH Priyadarshi
Veterinary Officer, Livestock Research Station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar, Gujarat, India

Clinicopathological studies on experimental toxicity of N-Butylbenzene Sulfonamide (NBBS) in Wistar rats (*Rattus Novergicus*)

BH Priyadarshi, DV Joshi, BJ Patel, SH Raval and HA Patel

Abstract
The present research work on clinicopathological studies on experimental toxicity of N-butylbenzenesulphonamide (NBBS) in Wistar rats was carried out on 80 wistar rats with 40 male and 40 female rats by dividing them into four equal groups, viz., Group I, II, III and IV. Group I served as control and received corn oil and Group II, III and IV were orally administered daily with N-butylbenzenesulphonamide at the dose of 10 mg/kg (low dose), 50 mg/kg (mid dose) and 250 mg/kg (high dose), respectively for a period of 90 days. All rats were subjected to haematology, biochemical profile and pathomorphological studies at the end of the experiment.

Haematology revealed no significant haematological changes were observed except significant ($p<$ 0.05) increase in mean values of platelets in Group III male rats and decrease in mean values of MCV and MCH in Group IV female rats as compared to control rats. Plasma biochemical profile revealed significant ($P<0.05$) increase in the values of ALT (Group IV), ALP (Group III) and Triglycerides (Group II, III) in male rats, whereas, there was significant ($p<$ 0.05) increase in AST (Group II, III,IV) , GGT (Group ,IV) , Urea (Group, IV) and Creatinine (Group, IV) values in female rats along with significant (P <0.05) decrease in Glucose (Group, IV).Varying degree of mild to moderate pathomorphological changes were observed mainly in liver, lung, kidney and adrenal gland. The microscopic lesions comprised of fatty changes and congestion in liver, tubular degeneration and tubular necrosis in kidney, congestion of alveolar capillaries with peribronchial and perivascular infiltration of inflammatory cells in Group IV rats. Multifocal alveolar histiocytic infiltration was noted in two males and one female of group IV. In addition, alveolar hemorrhages and congestion are also evident.

Keywords: N-butylbenzenesulfonamide, hematology, biochemical profile, peribronchial and perivascular infiltration of inflammatory cells, histiocytic infiltration, congestion, haemorrhage, Tubular degeneration

Introduction
N-butylbenzenesulfonamide (NBBS) is a common plasticizer used in polyacetals, polycarbonates, polysulfones and polyamides, in flexible tubing and in the production of films, transparent coating, and plastic resins [2]. NBBS is a plasticizer used for the polymerization of polyamide compounds in the production of plastic resins and as a starting agent in the synthesis of agricultural herbicides and fungicides [5]. Due to its widespread production and use, there may be significant potential for human exposure to NBBS, through ingestion, inhalation, and cutaneous routes. In addition to its plasticizer properties, NBBS possesses antifungal properties [1]. N-butylbenzenesulfonamide (NBBS) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological testing based on its extensive use as a plasticizer, lack of adequate toxicological data, and suspicion of toxicity based on the presence of structural alerts which suggest toxic effects [4]. Limited studies in rodents have shown NBBS exposure to cause neurotoxic and adverse developmental and reproductive effects. The benzensulfonamide substructure present in NBBS is a fairly common building block for industrial chemicals and drugs that have not been widely evaluated. There are insufficient toxicological data to adequately characterize potential human and animal health risks of NBBS. Nevertheless, different toxic potentials of NBBS have not yet been studied.

Keeping in the view, the present study was aimed to investigate the possible toxic effects of NBBS in Wistar rats with the broad objectives viz., to study the clinical symptoms and toxic manifestations, to analyse the hematological alterations, to analyse the blood biochemical profile and to study the pathomorphological changes in various organs.

The present study was carried out at the Department of Pathology, College of Veterinary Science and Animal Husbandry, Sardarkrushinagar on 40 male and 40 female healthy Wistar rats of 10-12 weeks age. Rats were acclimatized for 7 days under standard laboratory condition prior to experiment and randomly divided into four groups, Group I, II, III, IV. Each group consisted of 10 male and 10 female rats. The group I served as control and received only vehicle (Corn oil vehicle), while group II, III, IV received N-butylbenzenesulfonamide (NBBS) at doses of 10 mg/kg (low dose), 50 mg/kg (mid dose) and 250 mg/kg body weight (high dose), respectively, by oral gavage for 90 days of dosing period. The Oral administration of test article was made by gavage. The rats were observed daily observed for 90 days for clinical signs.

Haematological parameters were performed with auto blood analyser and included parameters as per Table 1, 2. The biochemical parameters included as per table 3, 4. On 91st day of study, all the rats were sacrificed by decapitation and were subjected to necropsy examination. The affected tissues preserved in 10 per cent neutral buffered formalin for at least 24 - 48 hours. Further, these tissues were processed using automated tissue processor (Leica TP 1020). Sections of 5µ thicknesses were cut with the use of automatic tissue microtome and stained by hematoxylene and eosin using automatic slide stainer (Thermo Scientific Gemini AS) for detailed histopathological alterations [2]. All data were subjected to stastical analysis using 2-way analysis of variance (ANOVA). Pair wise comparisons with control, for each sex separately, was made using Dunnett's test [5].

The results of haematological and biochemical parameters are presented in Table 1, 2, 3, 4. Clinical signs such as dullness, piloerection and excessive salivation were recorded in Group IV rats receiving toxic dose of NBBS. Haematological changes revealed no significant changes were observed except significant ($p< 0.05$) increase in platelets values in Group III male rats and decrease in MCV and MCH values in Group IV female rats as compared to control rats. Plasma biochemical profile revealed significant ($P<0.05$) increase in the values of ALT (Group IV), ALP (Group III) and Triglycerides (Group II, III) in male rats, whereas, there was significant ($p< 0.05$) increase in AST (Group II, III,IV) , GGT (Group, IV), Urea (Group, IV) and Creatinine (Group, IV) values in female rats along with significant ($P <0.05$) decrease in Glucose (Group, IV).

In the present study, no any appreciable macroscopic changes were noted in any organs in any groups except kidney, lung, liver and adrenal. Microscopically, moderate to mild lesions were noted in lung, liver, kidney and adrenal. Gross examination of lung from all the animals did not reveal any appreciable gross changes, except one female animal from Group IV showed multifocal, well demarcated, off white necrotic foci on lung parenchyma (Fig.1) which was considered as a incidental finding. Histopathological alteration in lung included hyperplasia of type II pneumocytes with infiltration of inflammatory cells in male rats (Fig.2), congestion of alveolar capillaries (Fig.3), focal perivascular infiltration of mononuclear cells and emphysema (Fig.4), focal infiltration of alveolar histiocytes (Fig.5) and alveolar emphysema and congestion in Group III female rats (Fig.6).

Histopathological changes in kidney were observed in mid dose (Group III) and high dose (Group IV). The lesions were characterised by glomerular necrosis (Fig.7), tubular degeneration with presence of proteinaceous cast in tubules (Fig.8), tubular necrosis with congestion (Fig.9). In addition to tubular degeneration and tubular necrosis, focal mononuclear cell infiltration (Fig.10) was also observed in male rat. Tubular haemorrhage (Fig.11) was also observed in one male rat of Group III.

Microscopic changes comprised of fatty change in liver characterised by vacuolation in hepatocytes with mild sinusoidal congestion (Fig.12), In the present study, no significant gross changes were observed in adrenal gland of any rats of treated as well as control group. Microscopic changes comprised of vacuolation (Fig.13) in one female rat of Group IV and congestion in one female rat of Group III (Fig.14).No appreciable pathomophological changes were observed in tissues like heart, brain, spleen, intestine, stomach, thymus, urinary bladder, sciatic nerve, mesenteric lymph node, pancreas, salivary gland, extra orbital lacrimal gland, uterus, cervix, epididymis, prostates, testes and ovary.

Reduction in haemoglobin values in this study was in accordance with findings of earlier reports [7, 8].There are no published reports on biochemical alterations in NBBS toxicity. AST is located in the cytosol but it is in higher concentrations in mitochondria. The significant increase in serum AST activity in female as observed in the current study may be due to hepatocellular injury. The significant increase in serum ALT value was observed in male rats of group IV. ALT activity is found in several body organs, but the magnitude of activity varies dramatically with species. ALT, primarily found in the cytoplasm of hepatocytes in liver. Serum ALT has been recognized as a marker of hepatocellular injury since the 1950s. Any injury to liver cells leads to increase in the serum level of ALT which was supported by histopathological alteration in liver as observed in the current study. Cells of liver, bone, kidney, intestinal mucosa, and placenta have the greatest ALP activity on a per gram of tissue basis with intestinal mucosa having the most. The significant increase in ALP activity as observed in present study is supported by the gross changes in intestine, liver and kidney in rats of current study. GGT is a membrane-bound enzyme on the external surface of cells and is bound to the cell membrane via a hydrophobic transmembrane peptide. Increase in serum values of GGT in high dose group is suggestive of injury to hepatocytes in liver which was in accordance with the histopathological changes observed in liver in present study [9].

In conclusion, the study revealed that the oral administration of N-butylbenzenesulfonamide (NBBS) for 90 days in Wistar rats were produced hematological and biochemical alteration in different treatment groups of rats with pathomorphological lesions were mild to moderate in nature and mainly found in liver, lung, kidney and adrenal glands.

Table 1: Effect N-butylbenzenesulfonamide (NBBS) on haematological parameters (Mean ± SD, n=10) in male rats after daily oral administration for 90 days.

Hematology Male						
Sr. No.	**Parameters**	**Unit**	**G I**	**G II**	**G III**	**G IV**
			0 mg/kg	**10 mg/kg**	**50 mg/kg**	**250 mg/kg**
1	Haemoglobin	g%	14.79±1.80[a]	15.19±1.32[a]	15.67±0.60[a]	14.32±1.71[a]
2	Hematocrit (HCT)	%	33.53± 7.43[a]	39.32± 3.88[a]	38.96±4.74[a]	34.11±9.98[a]
3	Total erythrocyte count (TEC)	10^6/µl	8.58±2.54[a]	7.24±2.61[a]	7.85±0.89[a]	7.17±1.96[a]
4	Mean corpuscles value (MCV)	g/fl	45.37±2.92[a]	44.16±15.64[a]	49.88±2.40[a]	42.27±8.69[a]
5	Mean corpuscles hemoglobin (MCH)	pg	17.98±3.51[a]	17.06±6.01[a]	19.28±0.78[a]	18.35±0.61[a]
6	Mean corpuscles hemoglobin concentration (MCHC)	g/dL	40.36±0.58[a]	36.89±14.26[a]	44.42±6.77[a]	40.45±0.89[a]
7	Total leukocyte count (TLC)	10^3/µl	5.55±2.46[a]	4.68±2.60[a]	4.72±2.66[a]	4.47±2.18[a]
8	**Differential leukocyte count (DLC)**					
	Neutrophils	10^3/µl	1.28±0.33[a]	1.16±1.04[a]	0.95±0.47[a]	1.47±0.92[a]
	Lymphocytes	10^3/µl	3.23±0.98[a]	2.96±1.48[a]	2.66±0.74[a]	2.16±1.03[a]
	Monocytes	10^3/µl	0.37±0.12[a]	0.41±0.31[a]	0.43±0.32[a]	0.17±0.18[a]
	Eosinophils	10^3/µl	0.31±0.23[a]	0.15± 0.27[a]	0.08±0.06[a]	0.20±0.19[a]
	Basophiles	10^3/µl	0.01±0.03[a]	0.00±0.00[a]	0.00±0.00[a]	0.01± 0.03[a]
9	Platelets	10^3/µl	780±258.08[a]	993.67±190.05[a]	1181±254.53[b]	632.60±62.79[a]
10	Red cell distribution width (%)	%	19.59±0.93[a]	18.23±6.45[a]	20.53±1.90[a]	19.90±0.79[a]
11	Red cell distribution width(a)	-	28.24±0.98[a]	31.33±1.612[a]	32.95±4.13[a]	27.470±1.62[a]
12	Mean Platelet volume	fl	5.46±0.49[a]	5.11±1.88[a]	5.60±0.69[a]	5.04±1.72[a]

- Superscripts are to be read row wise for mean comparison.
- Mean with similar superscripts in row do not differ significantly ($P < 0.05$).

Table 2: Effect N-butylbenzenesulfonamide (NBBS) on hematological parameters (Mean ± SD, n=10) in female rats after daily oral administration for 90 days.

Haematology Female						
Sr. No.	**Parameters**	**Unit**	**G I**	**G II**	**G III**	**G IV**
			0 mg/kg	**10 mg/kg**	**50 mg/kg**	**250 mg/kg**
1	Haemoglobin	g%	14.86± 0.57[a]	15± 0.95[a]	15.44±0.98[a]	14.42± 0.70[a]
2	Hematocrit (HCT)	%	37.40 ± 1.96[a]	37.46 ± 2.63[a]	38.43 ±2.45[a]	36.94 ± 1.21[a]
3	Total erythrocyte count (TEC)	10^6/µl	7.60± 0.31[a]	7.62 ± 0.45[a]	7.63± 0.53[a]	7.25 ±0.44[a]
4	Mean corpuscles value (MCV)	gm/fl	48.72± 1.73[a]	46.07± 1.06[a]	50.42±2.30[a]	32.42±15.75[b]
5	Mean corpuscles hemoglobin (MCH)	Pg	20.43 ±0.86[a]	20.82± 0.41[a]	20.87±0.87[a]	28.96±10.73[b]
6	Mean corpuscles hemoglobin concentration (MCHC)	g/dl	34.05± 1.38[a]	35.39±0.31[a]	36.48±1.42[a]	40.48±1.08[a]
7	Total leukocyte count (TLC)	10^3/µl	4.02± 0.35[a]	3.39± 1.25[a]	3.87± 1.06[a]	2.58±0.95[a]
8	**Differential leukocyte count (DLC)**					
	Neutrophils	10^3/µl	1.01± 0.48[a]	0.93± 0.27[a]	0.91±0.19[a]	0.66± 0.35[a]
	Lymphocytes	10^3/µl	2.70 ± 0.74[a]	2.03± 1.04[a]	2.45±0.79[a]	1.62±0.69[a]
	Monocytes	10^3/µl	0.27 ±0.08[a]	0.21± 0.07[a]	0.29± 0.12[a]	0.18± 0.08[a]
	Eosinophils	10^3/µl	0.21± 0.29[a]	0.16± 0.17[a]	0.27± 0.28[a]	0.20 ±0.20[a]
	Basophiles	10^3/µl	0.01± 0.03[a]	0.00 ± 0.00[a]	0.01± 0.03[a]	0.00 ± 0.00[a]
9	Platelets	10^3/µl	953.40± 106.80[a]	754.78±94.98[a]	703 ±295[a]	896.60±84.65[a]
10	Red cell distribution width (%)	%	19.68±0.54[a]	19.46± 0.39[a]	19.87±0.64[a]	19.84± 0.30[a]
11	Red cell distribution width(a)	-	24.46±5.38[a]	28.86± 3.64[a]	29.21±1.05[a]	30.20± 0.90[a]
12	Mean Platelet volume	fl	9.59± 0.03[a]	9.59± 3.03[a]	9.62± 0.04[a]	9.60± 0.00[a]

- Superscripts are to be read row wise for mean comparison.
- Mean with similar superscripts in row do not differ significantly ($P < 0.05$).

Table 3: Effect of N-butylbenzenesulfonamide (NBBS) on Biochemical parameters (Mean ± SD, n=10) in male rats after daily oral administration for 90 days.

Biochemical Data Male rats					
Parameters	**Unit**	**G I**	**G II**	**G III**	**G IV**
		0 mg/kg	**10 mg/kg**	**50 mg/kg**	**250 mg/kg**
Alanine aminotransferase (ALT)	U/L	53.83±17.32[a]	56.42±9.23[a]	36.37± 13.37[a]	93.24±38.24[b]
Aspartate aminotransferase (AST)	U/L	120.83±66.40[a]	150.78±75.95[a]	134.02±47.67[a]	107.44±38.90[a]
Gamma glutamyle transferase (GGT)	mg/dl	1.90± 1.661[a]	1.33± 0.59[a]	2.40± 1.01[a]	1.86±1.11[a]
Alkaline phosphatase (AKP)	U/L	116.7±32.95[a]	152.22±29.42[a]	158.80±30.68[b]	101.15±51.33[a]
Urea	g/L	54.42± 56.86[a]	28.42±6.09[a]	33.01± 6.85[a]	45.57±17.16[a]
Cholesterol	mg/dl	335.9±209.32[a]	133.44±6.17[a]	126.20± 4.08[a]	176±53.16[a]
Triglycerides	g/dl	146.5± 22.93[a]	174.78±9.83[b]	186.30± 5.03[b]	145.20±34.94[a]
Creatinine	mg/dl	0.23± 0.058[a]	0.24±0.05[a]	0.27±0.10[a]	0.33±0.18[a]
Total protein	g/dl	7.29±1.60[a]	5.68±0.59[a]	6.45±0.90[a]	6.28± 0.90[a]
Albumin	g/dl	4.36±0.32[a]	3.33±0.39[a]	3.78±0.41[a]	3.80±0.29[a]
Glucose	mg/dl	51.58±18.57[a]	39.84±1.23[a]	41.43±4.32[a]	56.63±10.41[a]

- Superscripts are to be read row wise for mean comparison.
- Mean with similar superscripts in row do not differ significantly ($P < 0.05$).

Table 4: Effect of N- N-butylbenzenesulfonamide (NBBS) on Biochemical parameters (Mean ± SD, n=10) in female rats after daily oral adm inistration for 90 days.

Biochemical Data Female rats					
Parameters	**Unit**	**G I**	**G II**	**G III**	**G IV**
		0 mg/kg	**10 mg/kg**	**50 mg/kg**	**250 mg/kg**
Alanine aminotransferase (ALT)	U/L	46.85±13.42[a]	56.79±8.63[a]	59.46±36.66[a]	45.56±23.06[a]
Aspartate aminotransferase (AST)	U/L	55.75±21.58[a]	122.73±45.04[b]	139±32.70[b]	149.30± 21.36[b]
Gamma glutamyle transferase (GGT)	mg/dl	1.69±0.73[a]	1.94±1.05[a]	1.80±1.19[a]	6.00± 1.24[b]
Alkaline phosphatase (AKP)	U/L	165.10±51.54[a]	185. 11± 71.66[a]	136.80±47.35[a]	148.20±52.46[a]
Urea	g/L	41.29±9.87[a]	22.12±4.63[a]	22.02±6.06[a]	42.28±5.17[b]
Cholesterol	mg/dl	126.90±11.97[a]	308.67±197.87[a]	129.60±11.07[a]	122.80±7.19[a]
Triglycerides	g/dl	153.60±12.27[a]	167±18.38[a]	166.90±23.44[a]	161.80±18.75[a]
Creatinine	mg/dl	0.37± 0.30[a]	0.27±0.08[a]	0.63±0.26[a]	0.95±0.41[b]
Total protein	g/dl	5.10±0.57[a]	4.57±3.30[a]	6.04±1.18[a]	6.26±2.35[a]
Albumin	g/dl	3.98±0.28[a]	6.79±0.81[a]	5.58±0.66[a]	5.50±0.53[a]
Glucose	mg/dl	53.16±10.09[a]	53.44±10.39[a]	47.43±12.66[a]	37.84±5.86[b]

- Superscripts are to be read row wise for mean comparison.
- Mean with similar superscripts in row do not differ significantly ($P < 0.05$).

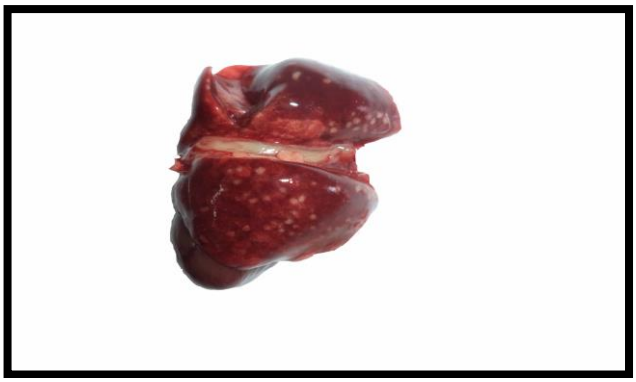

Fig 1: Group IV Female: Lung showing multifocal, well demarcated, off white necrotic foci

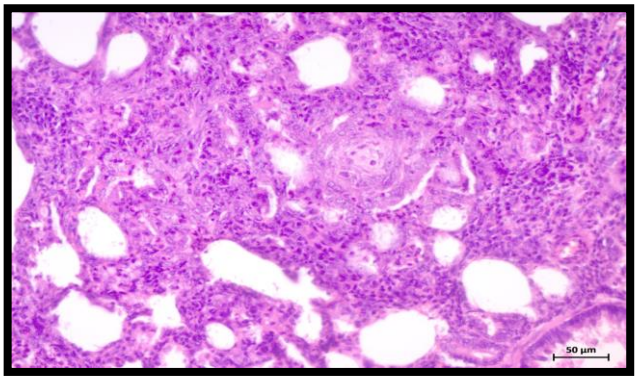

Fig 2: Group IV Male: Lung showing hyperplasia of type II pneumocytes with infiltration of inflammatory cells. (HE X 200)

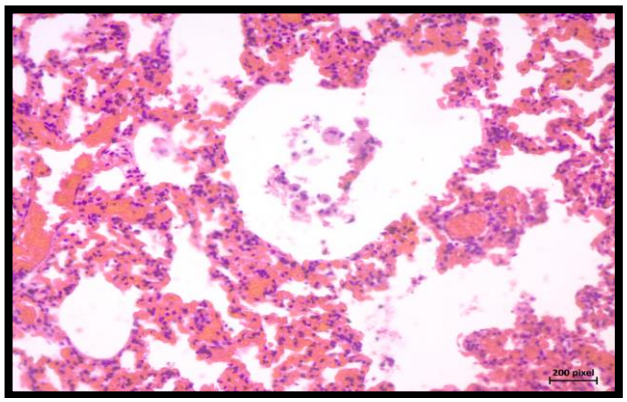

Fig 3: Group IV Male: Photomicrograph of lung showing congestion. HE X 200

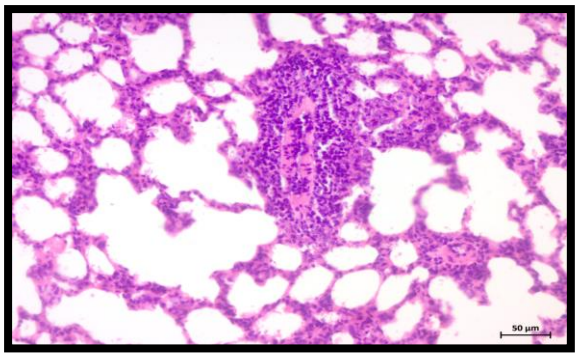

Fig 4: Group IV Male: Photomicrograph of lung showing perivascular infiltration of mononuclear cells and alveolar emphysema. (HE X 200)

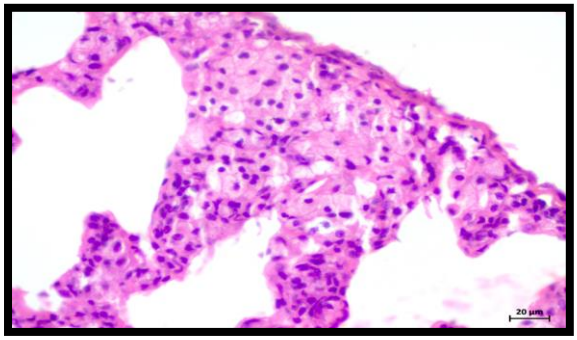

Fig 5: Group III Female: Photomicrograph of lung showing focal infiltration of alveolar histiocytes. (HE X 400)

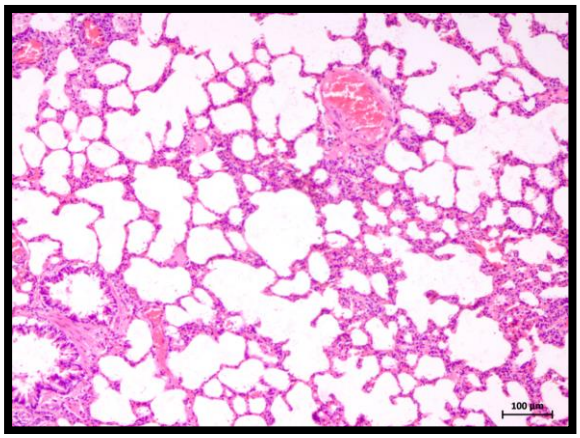

Fig 6: Group III Female: Photomicrograph of lung showing alveolar emphysema and congestion. (HE, X 100.

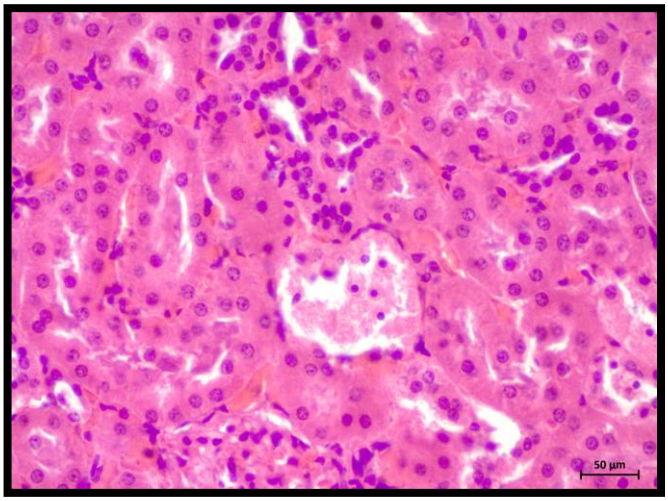

Fig 7: Group IV Female: Photomicrograph of kidney showing glomerular necrosis.
(HE X 200)

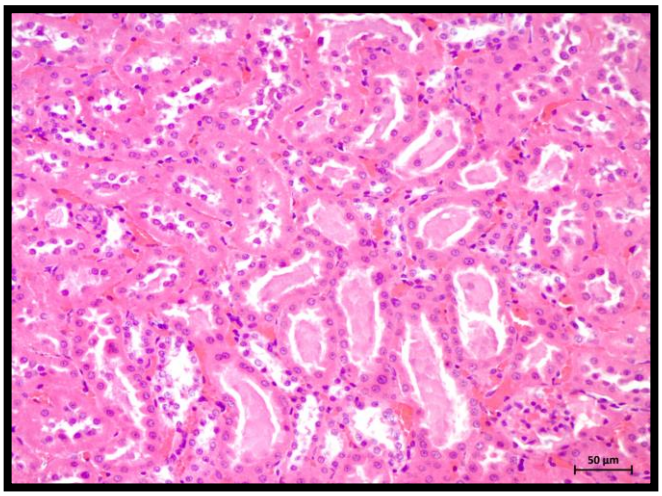

Fig 8: Group IV Male: Photomicrograph of kidney showing proteinaceous cast in tubules with congestion.
(HE X 200)

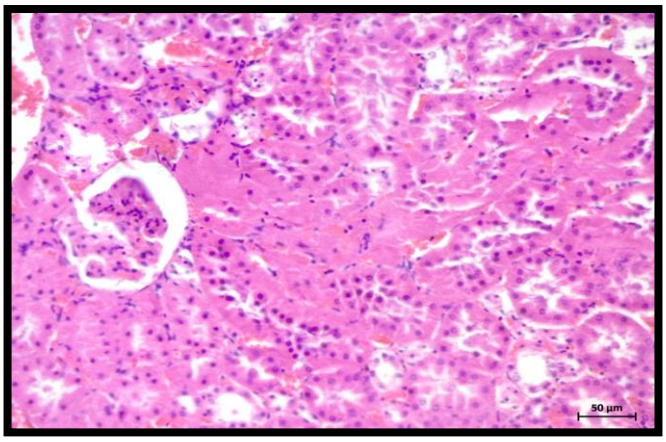

Fig 9: Group IV Male: Photomicrograph of kidney showing tubular necrosis with congestion.
(HE X 200)

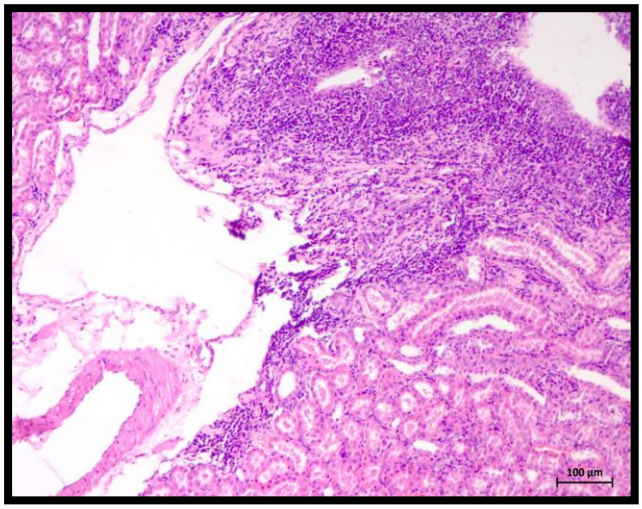

Fig 10: Group IV Male: Photomicrograph of kidney showing focal mononuclear cell infiltration along with tubular degenration.
(HE X 100)

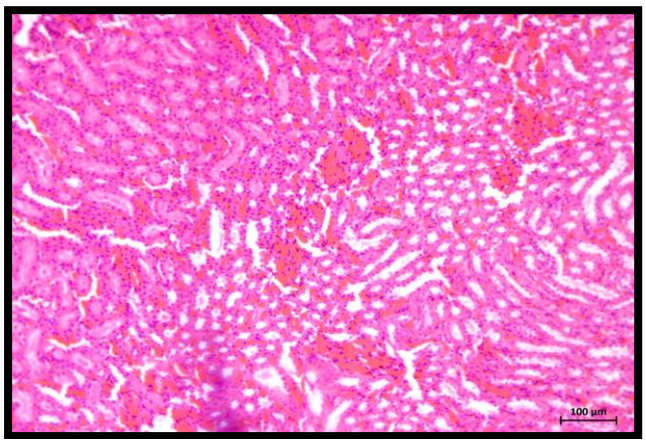

Fig 11: Group II Male: Photomicrograph of kidney showing tubular haemorrhage.
(HE X 100)

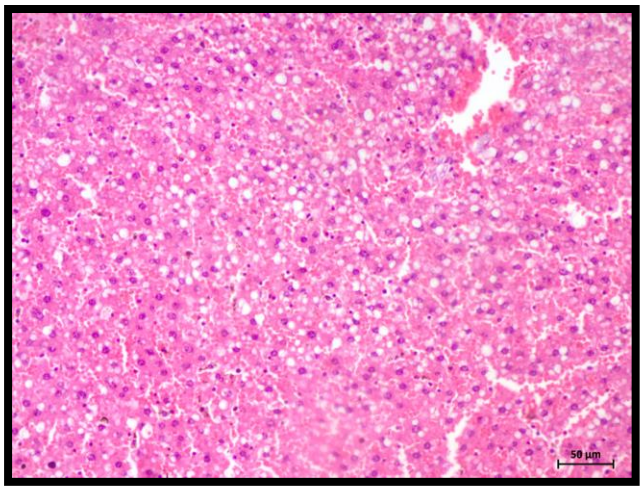

Fig 12: Group IV Female: Photomicrograph of liver showing vacuolation in hepatocytes with mild sinusoidal congestion.
(HE X 200)

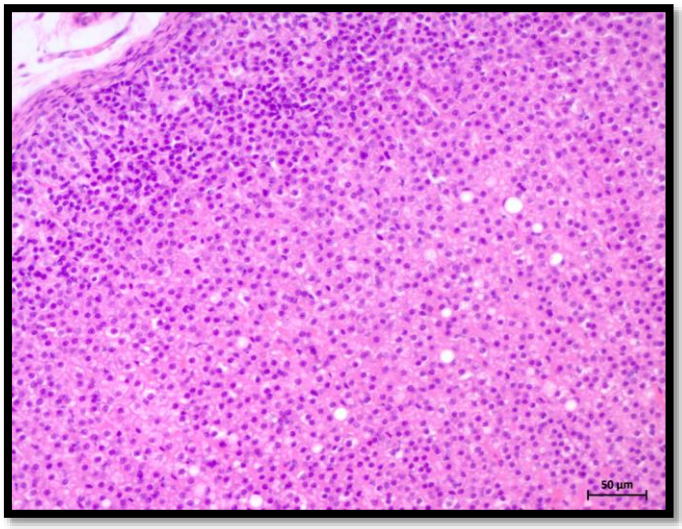

Fig 13: Group IV Female: Photomicrograph of adrenal gland showing vacuolation. (HE X 200)

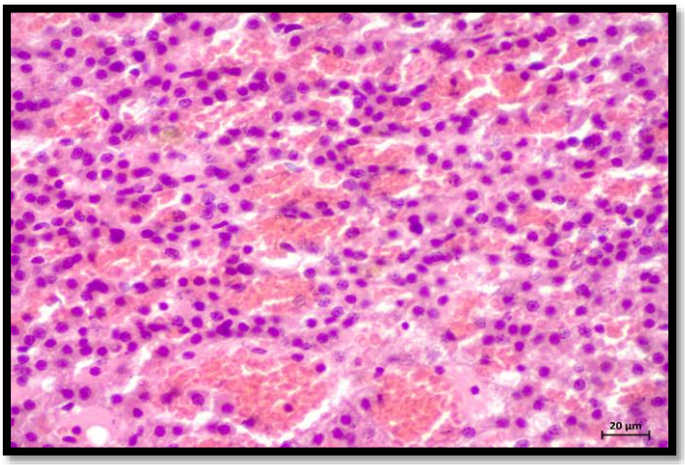

Fig 14: Group III Female: Photomicrograph of adrenal gland showing congestion. (HE X 400)

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