RESEARCH ARTICLE

Thallium Induced Sub-chronic Toxicity Profile in Wistar Rats

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Abstract

Thallium (Tl) is one of the most toxic heavy metals affecting both humans and animals, yet is one of the least studied for its toxicological effects. A total of 40 male Wistar rats were randomly divided into four Groups with 10 rats in each Group. Group I received distilled water only and served as a control. Group II, III, and IV received thallium sulfate (I) at 0.48, 0.93, and 1.33 mg/kg body weight, respectively, in drinking water for 90 days. In Group IV rats, lethargy, dehydration, weakness, mild diarrhea, weight loss and 100% morality were noted. Group II and III rats showed significant reduction in cholesterol, phosphorus, triglyceride level, and absolute and relative spleen weight. Microscopically, thallium sulfate (I) found to cause lymphoid depletion in white pulp of spleen in all treatment Groups. In kidney of Group IV rats, tubular necrosis, cytoplasmic vacuolation or clearing of tubules, cast, and thrombosis were found. Dose dependent hyperkeratosis was found in non-glandular stomach in all three treated Groups. In conclusion, spleen, kidney and stomach were primarily affected organs in sub-chronic thallium toxicity.

Keywords: Repeated 90 days study, Sub-chronic toxicity, Thallium sulfate (I), Wistar rats

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Introduction

Thallium (Tl; atomic number: 82) is a non-essential element and highly toxic heavy metal (density: 11.83 g/cm^3) found naturally in low concentrations in earth's crust. It is listed as priority environmental pollutant by the United States Environmental Protection Agency and the European Water Framework Directive (Belzile & Chen, 2017). Thallium exists in two oxidation states *viz*. Tl (I) or thallic or monovalent form (more stable) and T l(III) or thallous or trivalent form. Thallium in both states is toxic to human beings, domestic and wild organisms and acts as a cumulative poison (Rodriguez-Mercado & Altamirano-Lozano, 2013). Industrial as well as non-industrial thallium toxicity cases have been reported from different countries including India.

Before 1980s, thallium was used as insecticide, rodenticide (2% thallium sulfate), and chemotherapeutic agent to treat syphilis and gonorrhea but was discontinued later on due to its severe toxicity. The thallium poisoning cases is still reported in humans due to anthropogenic sources of thallium pollution (Cvjetko *et al*., 2010). Chronic thallotoxicosis are possible due to environmental exposure by consumption of contaminated vegetables and fruits growing in the vicinity of cement plants, coal incinerators and sulfuric acid factories (Anaya-Ramos *et al*., 2020). The physico-chemical properties of the thallium like colorless, partially water soluble and tasteless along with its affordability makes it a pick for malicious criminal purposes. The oral dose of 10-15 mg/kg body weight in humans may prove to be lethal (Zavaliy *et al*., 2021).

Fatal as well as survival thallium toxicity is also reported in the pet or companion animals. The wide spectrum clinical manifestations of thallium poisoning mainly include painful severe gastroenteritis, neurological, dermatological (alopecia is most common sign) and cardiovascular signs (Volmer *et al*., 2006; Puschner *et al*., 2012; Rodrigues *et al*., 2021). Thallium is able to cross the placental barrier and prenatal exposure to thallium, especially in first trimester, may increase the risk of adverse birth outcomes such as preterm delivery and low birth weights (Wu *et al*., 2019).

Thallium is underestimated and understudied metal with regard to its toxicity (Cvjetko *et al*., 2010). The 90-days sub-chronic toxicity studies in rodents are important to assess the target organs involved as an important tool of risk assessment. Since, such studies are lacking for the long-term thallium oral exposure, the present study was undertaken to know the sub-chronic toxicity profile of thallium in Wistar rats at three different dose rates.

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Materials and Methods

Ethical Statement: The present study was duly approved by Institutional Animal Ethics Committee (IAEC) *vide* research protocol no. VETCOLL/IAEC/2019/14/PROTOCOL-No.10.

Animals and Experimental Design

Wistar rats used in the study were procured from the Laboratory Animal Facility, Torrent Research Centre, Ahmedabad, Gujarat. Animal management and treatment procedures complied with the standard guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi. In the present study, thallium sulfate (I) (Tl_2SO_4: Sigma Aldrich) was used. All the 40 male rats were randomly divided into four groups (group I to IV), each group consisted of 10 rats. Group I or control group received vehicle (distilled water) only. Thallium sulfate was dissolved in distilled water at 6.25, 12.50, and 25.0 mg/L of water and given orally to Group II, III, and IV, respectively, equivalent to 0.48, 0.93 and 1.33 mg/kg body weight/daily.

Clinical Observations

Observations for morbidity and mortality were made twice daily throughout the study. The live body weights were recorded at day one of initiation of dosing and thereafter at weekly intervals throughout the study period. Relative organ weight was calculated on basis of terminal body weight recorded before necropsy.

Terminal Body and Organ Weight

Brain, stomach, intestines, liver, kidneys, adrenals, spleen, heart, thymus, trachea, lungs, prostate, seminal vesicles, urinary bladder, testis and epididymis were collected in 10% neutral buffered formalin. The liver, kidneys, adrenals, thymus, spleen, brain, heart, epididymis, and testis of all survived rats were trimmed for any adherent tissue, and wet weight was taken immediately after dissection.

Clinical Pathology

On study day 91, blood was collected from the retro-orbital plexus of all survived rats in clot activator for clinical chemistry and EDTA for haematological investigation. Haematological parameters (RBC, Hb, HCT, MCV, MCH, MCHC, Platelet count, WBC, and DLC) were analyzed on the day of collection using a fully automatic veterinary hematology analyzer (Exigo™ EOS, Boule Diagnostics AB, Sweden). Blood smears were prepared within 3 h of collection and stained with Giemsa for manual evaluation of platelet, erythrocyte morphology and basophils count. Biochemical parameters (ALT, AST, ALP, Total Protein, Albumin, Urea, Creatinine, Triglyceride, Phosphorus, Calcium, Magnesium, Cholesterol and GGT) were analyzed using a fully automatic clinical chemistry analyzer (Randox-Monaco, Randox Laboratories Ltd., United Kingdom).

Tissue Processing for Histopathology

Group IV rats were observed every 8 h for any mortality , if any rat found dead it was soon processed for postmortem and collection of tissues for histopathology. Fixed tissues were subjected to routine tissue processing as per standard protocol. They were embedded in paraffin blocks using the Leica EG1160 paraffin embedding station. The sections of 5µ thickness were obtained using Leica RM2255 fully automated rotary microtome and stained with Harris' Hematoxylin and Eosin (H&E stain). The entire staining was performed in Gemini AS Automated Slide Stainer (Thermo Scientific). Stained tissue sections were examined under light microscope after DPX mounting.

Statistical Analysis

The statistical analysis of data generated on body weights, haematological and biochemical parameters, absolute and relative organ weights, was subjected to statistical analysis using Two-way analysis of variance (ANOVA) and Dunnett's test.

Results and Discussion

Clinical Observations, Mortality Pattern & Body Weight

Rats of Group II did not show any noticeable clinical signs throughout the 90 days and were comparable to control rats (Group I). The rats of Group III and IV showed initial clinical signs like partial hair loss in forehead. Stoltz *et al.* (1986) observed similar hair losses in thallium sulfate treated rats. Beside hair losses, they also noted lacrimation and exophthalmos in treated rats, which was not observed in the present study. At 90-days, Group III rats showed lesser activity when compared with control rats. Group IV rats showed lethargy with minimal activity, dehydration, weakness, mild diarrhoea, and weight loss.

In the present study, there was no mortality in Group I, II, and III, however, all the ten rats of Group IV were died in phases, on study days 47 (n=4), 48 (n=1), 63 (n=1), 64 (n=1), 68 (n=2), and 82 (n=1). In rats, LD_{50} of thallium compounds were reported as 32 mg/kg (thallium acetate) and 39 mg/kg (thallic oxide). For thallium sulfate, a daily dose of 1.4 mg thallium/kg/day in drinking water caused 15 – 21 % mortality (ATSDR, 1992). In the present study, Group II and III rats did not show any mortality which is in accordance with report of Stoltz *et al.* (1986) who also did not find any morality in rats administered with thallium sulfate at the oral dose rate of 0.2 mg/kg for 90 days. The effect of thallium administration on body weight is presented in Table 1. Statistical comparison were made for body weights upto 42 days, as on day 47 and onward there was mortality noted in Group IV. There was statistically significant ($p < 0.05$) decrease observed in body weights of Group IV rats on the days 35 and 42. However, in a study report by Midwest Research Institute, USA, there was no statistically significant differences in body weight of Sprague-Dawley rats orally receiving an aqueous solution of thallium (I) sulfate (0.01, 0.05, or 0.25 mg/kg b.wt./day) for 90 days (MRI, 1988).

Haemato-biochemical Findings

The mean values of various haematological and biochemical parameters of Group I, II and III rats on the completion of study (Day 91) are presented in Table 2 and 3, respectively. Such data set for Group IV was obviously not obtained due to mortality of all rats before day 90. In the present study, no statistically significant difference in the haematology data was observed for any treatment group when compared to control Group (I) rats. Haematological observations of the present study are in accordance to the previous report, wherein 0.25 mg/kg or less thallium sulfate oral administration in Wistar rat for 30 or 90 days did not alter haematology parameters (MRI, 1988).

Table 1: Effect of thallium sulfate (I) on weekly body weight (g) (Mean ± SD) in male rats after daily oral administration for 42 days (n=10)

Day	*Group I 0 mg/kg*	*Group II 0.48 mg/kg*	*Group III 0.93 mg/kg*	*Group IV 1.33 mg/kg*
0 Day	569.80 ± 49.52	569.50 ± 42.16	583.56 ± 47.82	567.25 ± 40.38
7 Day	573.80 ± 45.35	579.80 ± 40.43	599.09 ± 51.48	562.72 ± 37.46
14 Day	572.35 ± 42.53	579.35 ± 40.53	601.73 ± 50.75	557.40 ± 36.96
21 Day	579.21 ± 42.72	582.31 ± 41.78	602.34 ± 56.50	551.04 ± 35.97
28 Day	589.16 ± 41.19	591.35 ± 44.11	604.62 ± 60.16	545.16 ± 35.85
35 Day	594.78 ± 42.34	598.37 ± 46.78	608.34 ± 65.68	537.13 ± 37.83*
42 Day	604.78 ± 45.06	607.17 ± 46.17	612.04 ± 70.25	518.22 ± 35.22*

*Statistically significant changes in body weights were observed ($p < 0.05$) on day 35 and 42.

Table 2: Effect of thallium sulfate (I) on haematological parameters (Mean ±SD) in male rats after daily oral administration for 90 days (n=10)#

Haematological Parameters	*Unit*	*Group I 0 mg/kg*	*Group II 0.48 mg/kg*	*Group III 0.93 mg/kg*
RBC	10^6/µL	7.33 ± 1.02	7.33 ± 1.64	7.72 ± 0.48
Hb	g/dL	14.90 ± 0.49	15.31 ± 0.65	15.23 ± 0.95
HCT	%	45.10 ± 7.40	47.63 ± 10.62	37.75 ± 6.25
MCV	fL	61.23 ± 5.53	60.80 ±12.67	53.55 ± 4.97
MCH	pg	20.76 ± 3.64	18.96 ± 0.86	19.68 ± 0.59
MCHC	g/dL	34.07 ± 6.25	29.23 ± 1.74	34.27 ± 1.99
Platelet count	10^3/µL	1169.50 ± 307.97	1203.30 ± 429.67	1327.60 ± 154.95
WBC	10^3/µL	4.51 ± 0.99	4.09 ± 0.93	4.86 ± 0.68
Neutrophils	%	6.53 ± 3.70	8.67 ± 5.09	6.98 ± 5.03
Lymphocytes	%	89.95 ± 4.31	87.88 ± 5.54	89.59 ± 5.79
Monocytes	%	2.42 ± 0.78	2.35 ± 0.56	2.33 ± 0.59
Eosinophils	%	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Basophils	%	0.10 ± 0.32	0.10±0.32	0.10±0.32

#No statistically significant changes in body weights were observed ($p > 0.05$)

In the present study, statistically significant reduction in cholesterol, phosphorus, and triglyceride was noticed in Group II and III treated rats. In contrast to present findings, Mourelle *et al*. (1988) reported significant increase in triglycerides levels post 48 hours of treatment with thallium (I) sulfate administration in male Wistar rats.

Thallium can substitute K^+ ion in Na^+/K^+-ATPase with a tenfold greater affinity for this enzyme which ultimately inhibit the Na^+/K^+-ATPase pump activity (Cvjetko *et al*., 2010; Genchi *et al*. 2021). Alteration in such pump activity may interfere with intracellular and extracellular homeostasis of calcium and phosphorus, which may be a reason for reduced level of phosphorus due to thallium administration in the present study. Thallium ions interact with membrane phospholipids and other lipid molecules (Villaverde and Verstraeten, 2003) which may be the reason for the alterations in the level of triglycerides found in the study. There was a numerical decrease in AST and ALP, but statistically no significance changes were observed in present study. However, in previous studies, AST, ALT, creatinine, urea nitrogen, and ALP were reported to be increased due to thallium intoxication (Stoltz *et al*., 1986; Leung and Ooi, 2000).

Table 3: Effect of thallium sulfate (I) on biochemical parameters (Mean ± SD) in male rats after daily oral administration for 90 days (n=10)

Biochemical Parameter	*Unit*	*Group I* *0 mg/kg*	*Group II* *0.48 mg/kg*	*Group III* *0.93 mg/kg*
ALT	U/L	30.95 ± 6.44	30.51 ± 3.53	31.37 ± 4.91
AST	U/L	143.79 ± 31.55	116.72 ± 26.55	119.35 ± 8.81
ALP	U/L	101.62 ± 22.98	91.09 ± 13.18	85.73 ± 13.10
Total Protein	g/dL	7.83 ± 0.20	7.74 ± 0.30	7.66 ± 0.12
Albumin	g/dL	3.54 ± 0.11	3.58 ± 0.08	3.50 ± 0.07
Urea	mg/ dL	60.93 ± 7.81	63.26 ± 6.31	62.50 ± 11.02
Creatinine	mg/ dL	1.77 ± 2.54	0.90 ± 0.07	0.91 ± 0.09
Triglyceride	mg/ dL	180.30 ± 41.28	129.06 ± 52.07*	122.67 ± 43.74*
Phosphorus	mg/ dL	8.04 ± 1.37	6.82 ± 0.46*	5.80 ± 0.84*
Calcium	mg/ dL	12.03 ± 0.83	11.92 ± 1.00	11.44 ± 0.30
Magnesium	mg/ dL	6.29 ± 0.26	6.26 ± 0.13	6.11 ± 0.20
Cholesterol	mg/ dL	117.23 ± 16.69	89.26 ± 12.21*	83.72 ± 11.68*
GGT	U/L	0.50 ± 0.71	0.40 ± 0.70	0.30 ± 0.48

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl Transferase
* Differences were considered statistically significant when $p < 0.05$

Table 4: Effect of thallium sulfate (I) on absolute organ weight (Mean ± SD) in male rats after daily oral adminitastration for 90 days

Organ	*Group I* *0 mg/kg*	*Group II* *0.48 mg/kg*	*Group III* *0.93 mg/kg*
Liver	16.10± 1.502	15.97±1.788	17.34±2.764
Spleen	1.07± 0.125	0.910±0.100*	0.78±0.085*
Heart	1.47± 0.272	1.59±0.203	1.46±0.271
Testes	3.84±0.482	3.45±0.673	3.99±1.047
Kidneys	3.21±0.353	3.45±0.325	3.62±0.648
Brain	2.21±0.107	2.13±0.146	2.23±0.128
Thymus	0.22±0.078	0.23±0.031	0.16±0.044
Epididymis	1.59±0.218	1.68±0.295	1.65±0.393
Adrenals	0.08±0.015	0.09±0.009	0.08±0.009

*Differences were considered statistically significant when $p < 0.05$

Table 5: Effect of thallium sulfate (I) on relative organ weight (Mean ± SD) in male rats after daily oral administration for 90 days

Organ	*Group I* *0 mg/kg*	*Group II* *0.48 mg/kg*	*Group III* *0.93 mg/kg*
Liver	2.56±0.147	2.54±0.219	2.81±0.419
Spleen	0.17±0.026	0.14±0.018*	0.12±0.021*
Heart	0.23±0.030	0.25±0.039	0.23±0.032
Testes	0.61±0.063	0.55±0.119	0.64±0.098
Kidneys	0.51±0.045	0.55±0.050	0.56±0.045
Brain	0.35±0.018	0.33±0.019	0.36±0.033
Thymus	0.03±0.013	0.03±0.006	0.03±0.009
Epididymis	0.25±0.045	0.27±0.057	0.26±0.037
Adrenals	0.01±0.003	0.01±0.002	0.01±0.002

* Differences were considered statistically significant when $p < 0.05$

Absolute and Relative Organ Weights

The effect of oral administration of thallium (I) sulfate on absolute and relative organ weight is summarized in Table 4 and 5 respectively. In the present study, all Group IV rats (receiving high dose) died before 90 days hence, their absolute and relative organ weight could not be not recorded. Statistically significant decrease in absolute and relative weight was observed for spleen only, in rats of the Group II and III. Similar findings, except spleen, were also reported in other studies (Stoltz *et al*., 1986; MRI, 1988). In contrast to our findings, Leloux *et al.* (1987) reported increase in the absolute weight of kidneys in male and female rats administered with thallium (I) nitrate.

Histopathological Findings

In the present study, spleen of group I control rats showed normal interconnected white pulp with prominent periarteriolar lymphoid sheaths (Fig. 1) whereas spleen of Group IV rats showed lymphoid depletion characterized by loss of lymphocytes and macrophages from marginal zone as well as periarterial lymphatic sheaths (Fig. 2). Similar lesions had been noted in Group II and III.

Microscopically, kidney of Group IV rats showed tubular necrosis, cytoplasmic vacuolation of tubules, cast, and thrombosis as compared to kidneys of control group rats. Tubular necrosis was predominantly noted in outer medulla and characterized by loss of epithelium cells with accumulation of eosinophilic amorphous luminal debris in tubular lumen (Fig 3 and Fig 4). Various mechanisms of toxicity proposed for thallium include mitochondrial damage, cellular oxidative stress, production of reactive oxygen species, blocking cell cycle progression clubbed with inhibition or dysregulation of Na^+/K^+- ATPase and interference with energy production (Cvjetko *et al*., 2010; Osorio-Rico *et al*., 2017). Dysregulation of Na^+/K^+-ATPase pump may be responsible for cytoplasmic vacuolation of renal tubules found in the present study.

In non-glandular stomach, thallium administration induced orthokeratotic or parakeratotic hyperkeratosis in Group IV animals. In comparison to control group rats (Fig. 5), Group IV rats showed diffuse thickening of stratum corneum with or without retention of nuclei. Stratified squamous epithelium showed dyskeratosis characterised by abnormal keratinization (Fig. 6).

The histopathology of pulmonary tissues from Group IV rats revealed mild congestion and oedema in lungs (Fig. 7). In liver of all treatment groups, no significant changes were found related to thallium toxicity. However, in Group II rats, one rat showed focal hepatocellular necrosis (Fig. 8) and was considered as incidental finding.

Conclusions

Thallium sulfate(I) administered at the dose rate of 1.33 mg/kg body weight in Wistar male rats induced 100% morality within 82 days. There was statistically significant decrease in body weight of Group IV rats on days 35 and 42. Thallium sulfate(I) administered at 0.48 mg/kg body weight or higher, induced statistically significant reduction in cholesterol, phosphorus and triglyceride level, and absolute and relative spleen weight. Based on histopathological findings, spleen, kidney, and stomach were major target organs of thallium sulfate(I) intoxication.

Acknowledgement

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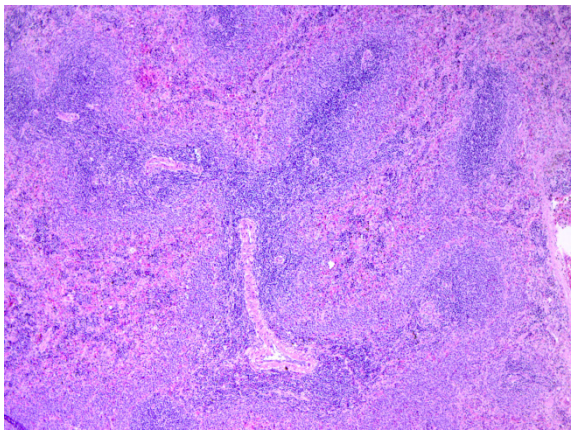

Figure 1: Group I. Photomicrograph of section of spleen showing normal interconnected white pulp with prominent periarteriolar lymphoid sheaths (PALS) and marginal zone. H&E 50X.

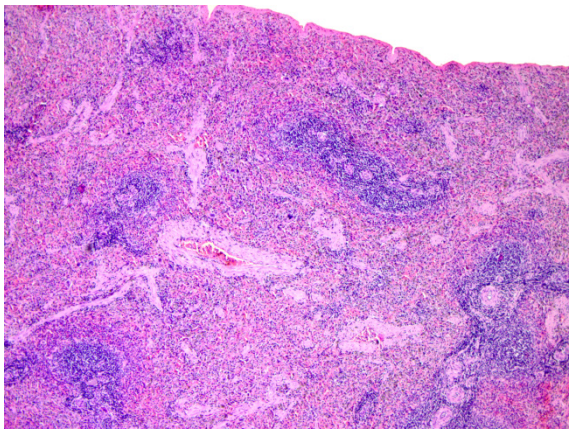

Figure 2: Group IV. Photomicrograph of section of spleen showing increased distance between the white pulp due to moderate atrophy of white pulp. H&E 50X.

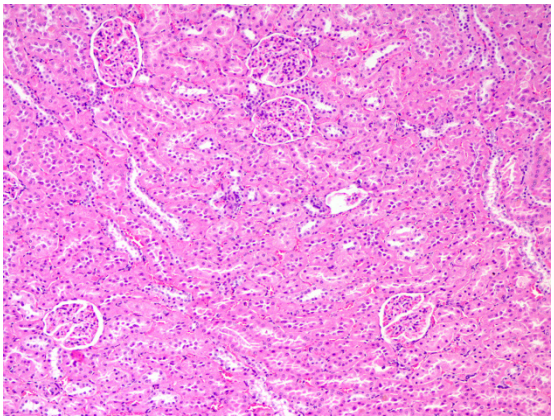

Figure 3: Group I. Photomicrograph of section of normal Kidney (Control Group). H&E 100X.

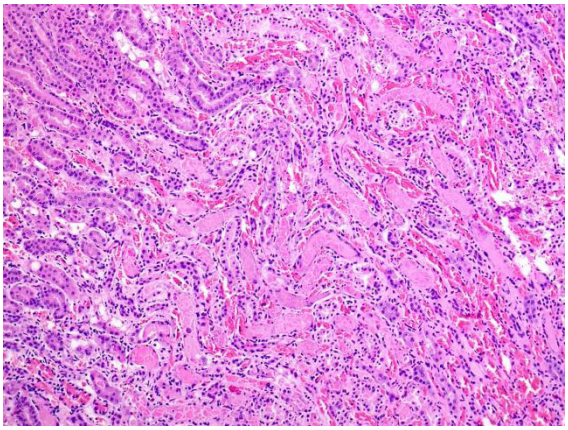

Figure 4: Group IV. Photomicrograph of section of kidney showing tubular necrosis in outer medulla, characterized accumulation of eosinophilic amorphous luminal debris in tubular lumen and loss of lining epithelium. H&E 100X.

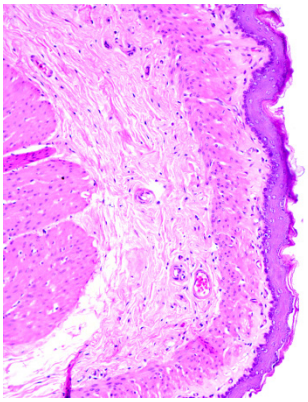

Figure 5: Group I. Photomicrograph of section of non-glandular stomach showing normal stratified squamous epithelium with thin keratin layer. H&E 100X.

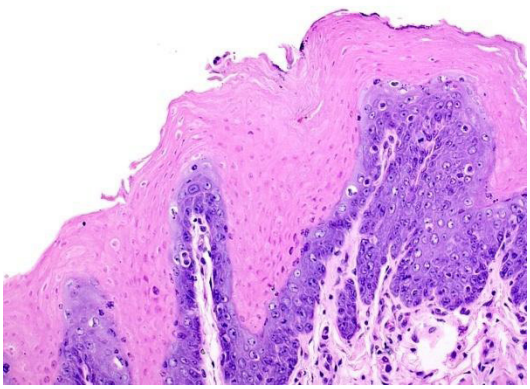

Figure 6: Group IV. Photomicrograph of section of non-glandular stomach showing parakeratotic hyperkeratosis, single cell necrosis, and dyskeratosis. H&E 200X.

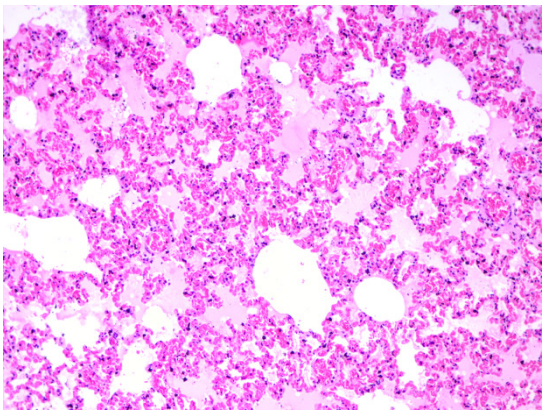

Figure 7: Group IV. Photomicrograph of section of lung showing multifocal alveolar edema and congestion. H&E 100X.

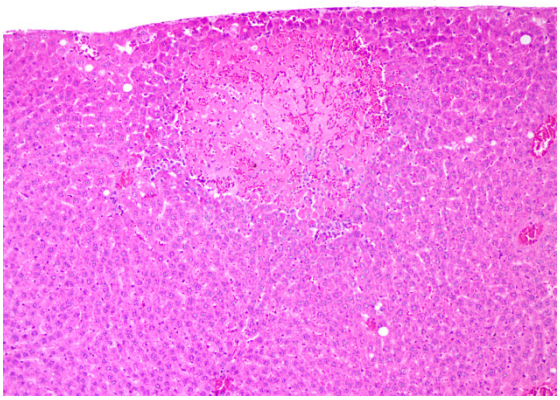

Figure 8: Group II. Photomicrograph of section of liver showing focal hepatocellular necrosis. H&E 100X.

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