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ISSN 2250-3153

28 day repeat dose (sub-chronic) toxicity of recombinant Enfuviritide on New zealand white rabbits

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Abstract- Enfuvirtide is a first of its class as a fusion inhibitor drug which inhibits the fusion of HIV-1 virus with CD4+ cells on the target organism with a human therapeutic dose of 90mg/twice daily. It is a linear 36 amino acid peptide with the empirical formula $C_{204}H_{30}N_{51}O_{64}$, and the molecular weight of 4.4Kd. The present study was conducted to investigate the repeat dose toxicity of recombinant Enfuvirtide, which was manufactured in-house, when administered twice daily subcutaneously for twenty eight consecutive days in New Zealand white rabbits at dose levels of 4.2 mg/kg bw (Therapeutic Dose), 10.5 mg/kg bw (Average Dose) and 21.0 mg/kg bw (High Dose) in comparison with synthetic enfuvirtide. The animals were observed during this period for mortality/morbidity, clinical signs, body weight, food consumption, hematology and clinical chemistry. At the end of the experimental period all the animals were necropsied and vital organs were weighed and subjected to histopathological examination. In conclusion, No repeated administration of recombinant Enfuvirtide for a period of 28 days did not exert any toxic effects in rabbits at different dose levels.

Index Terms- 28-Day Subchronic Oral Toxicity, Enfuvirtide, HIV-1Virus, NewZealand White Rabbits, OECD Guidelines Test No.407.

I. Introduction

The use of synthetic peptides as HIV-1 inhibitors has been the object of research over recent years. A large number of peptides that affect different stages of the HIV-1 life cycle have been and continue to be studied due to their possible clinical application in the fight against HIV-1 infection. The main advantages of synthetic peptides as therapeutic agents are their low systemic toxicity, the fact that structural modifications can be made to them and their resulting capacity to mimic certain substrates or epitopes. HIV-1-inhibiting peptides have been identified and/or developed using different methods.

Although combination antiretroviral therapy has dramatically improved the lives of patients with human immunodeficiency virus (HIV) infection, viral strains that are resistant to multiple medications are a serious problem. The durability of suppression of human immunodeficiency virus (HIV) infection with antiretroviral therapy is often limited, for reasons that include poor penetration into protected sites containing a reservoir of HIV [1], drug toxicity [2], alterations in the bioavailability and metabolism of antiretroviral drugs (e.g., interactions between drugs) [3] and lack of adherence to complex treatment regimens [4]. These factors contribute to persistent viral replication in patients receiving therapy, increasing the risk of viral resistance, which can limit future treatment options [5].

Enfuvirtide (also known as T-20) is a novel, synthetic, 36-amino-acid peptide that binds to a region of the envelope glycoprotein 41 of HIV type 1 (HIV-1) that is involved in the fusion of the virus with the membrane of the CD4+ host cell [6]. This agent exhibits potent and selective inhibition of HIV-1 in vitro without cytotoxicity [7] and is the first inhibitor of HIV entry to show consistent potent activity in persons infected with HIV-1[8]. Enfuvirtide interferes with the entry of HIV-1 in to cells by inhibiting fusion of viral and cellular membranes. The HIV-1 viral envelope glycoprotein consists of two noncovalently associated subunits, a surface glycoprotein (gp120) and a transmembrane glycoprotein (gp41) [9]. Gp41 undergoes conformational rearrangements which accelerates the fusion of viral and cellular membranes that causes viral entry into the host and integrates into the host genome and finally express it. As a result the formation of six helix bundle, viral and cellular membrane comes together and allowing them to fuse with each other. Recombinant Enfuvirtide, binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes [10].

Enfuvirtide originated at Duke University and the development of enfuvirtide was started in 1996 and initially designated as **T-20**. It was approved by the U.S. Food and Drug Administration (FDA) on March 13, 2003 as the first HIV fusion inhibitor, a new class of antiretroviral drugs. Since the production of T20 by synthetic methods is expensive and cumbersome, an alternative recombinant approach for the production of the T20 peptide through a novel short fusion-tag expression system has been reported [11]. Moreover, the treatment with T20 involves high therapeutic doses. Production of therapeutic products by the rDNA technology has several advantages, such as provision of drugs that could not be produced by conventional methods, manufacture of sufficient quantities of drugs at lower cost, lowers the manufacturing cost and steps involved in the production of the drug and provision for manufacturing safe drugs.

Although several articles are available regarding the pharmacological activity of the product, literature regarding the safety profile is scarce. Hence, the current study was carried out to assess the repeat dose toxicity effects of recombinant Enfuvirtide, when administered subcutaneously for a period of 28 days to male and female New Zealand White Albino Rabbits at various dose levels as mentioned in the test system. Rabbits were selected as the testing species because one rodent and one non-rodent are mandatory as per the regulatory requirement. The dose levels were calculated based on the body surface area

(BSA) ratio factor, and the route of administration of test compound is subcutaneous which was similar to that of innovator's synthetic enfuvirtide (Brand name: Fuzeon, Roche Laboratories Inc.,).

II. MATERIALS AND METHODS

EthicalClearance **-** The study was carried out in compliance with the 'Guidelines for Laboratory Animals Facility' issued by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. These guidelines promote the humane care of animals used in research by providing specifications that will enhance animals' well being and experimental quality for the advancement of biological knowledge that is relevant to humans and animals.

Institutional Animal Ethics Committee (IAEC) had recommended and CPCSEA had approved the project proposal.

Experimental Conditions

Animal Husbandry **-** The conduct of a repeat dose oral toxicity study is a requirement of worldwide drug regulatory agencies [12-15] for intended use in humans. Rabbit is a standard non rodent species used in toxicology studies based upon the substantial amount of published historical data on the suitability for such studies. The number of animals used in this study is based upon worldwide regulatory guidelines [12-15].

Animals were allowed to acclimatize to the experimental conditions for a period of 7 days prior to treatment. During the acclimatization period, the animals were observed daily for clinical signs of any existing disease. Prior to grouping, a detailed physical examination was performed on all the experimental animals. Animals were maintained in an environment-controlled room at a temperature of 20 ± 3 °C and relative humidity of 30 to 70 per cent. Rabbits were housed individually. The experimental animals were fed *ad libitum* with standard pellet feed and Lucerne grass.

Route of administration **-** Recombinant Enfuvirtide was administered subcutaneously as it is the recommended route of administration in humans.

Experimental procedure - Animals were randomized into 7 groups and the test compound was administered to each group of 3 males and 3 females twice daily, subcutaneously for a period of 28 days. After 28 days of repeated administration, animals from group I (VC), II (TD), III (TD(I)), IV (AD) and V (HD) were sacrificed and tissues and blood samples were collected and stored for further investigations. The two additional satellite groups i.e. Group VI and Group VII (Satellite VC and HD) were observed for reversibility, persistence, or delayed occurrence of toxic effects for a post treatment of 14 days. The recovery group animals were sacrificed on day 43 and various investigations were conducted as per the schedule.

Dosing **-** Formulated recombinant Enfuvirtide in dose levels of 4.2 mg/kg bw (Therapeutic Dose), 10.5 mg/kg bw (Average Dose) and 21.0 mg/kg bw (High Dose and Satellite High Dose) twice daily for a period of 28 days. Vehicle Control groups (Vehicle Control and Satellite Vehicle Control) were administered with formulation buffer. Animals were observed for a period of 28 days till the last administration of the test compound.

Observations **-** Mortality rate, In-life and cage side examinations were done regularly, hematology, clinical chemistry was carried on day 0 and day 29 for main groups and on day 0 and 43 for recovery groups. Gross necropsy was performed on both main group and recovery group animals. Brain, thymus, spleen, bone marrow, kidney, wound site/ site of application, heart, lung, trachea, thyroid, sternum, liver, gastro intestinal tract, testes and ovaries were collected from all the animals and preserved in 10% buffered neutral formalin for histopathological analysis

Statistical Analysis **-** Treatment groups were compared with vehicle control by Fisher's exact or Chi-square test. Between group comparisons by means of Kruskal-Wallis one-way ANOVA and individual group comparisons by Mann-Whitney U test (treatment groups with vehicle control) were the method of analysis. Two-tailed probability level of 0.05 was set in these experiments for rejecting the null hypothesis.

III. RESULTS AND DISCUSSION

Recombinant Enfuvirtide was administered twice a day subcutaneously to Newzealand white rabbits for a period of 28 days at different dose levels. In comparison with the vehicle control and Innovator therapeutic group Enfuvirtide did not show any significant changes in the in physical and physiological parameters which were assessed throughout the experimental period.

All the male and female animals from control and all the treated dose groups survived throughout the dosing period of 28 days and the recovery period of 14 days. No signs of intoxication were observed in male and female rabbits of main and recovery groups during the 28 days dosing period and 14 day recovery period. Local tolerance of recombinant Enfurvirtide was evaluated as a clinical observation and morphologic pathology of injection site. No adverse effects such as irritation, inflammation and edema were noticed at the site of injection. No treatment related weight loss was observed in all the animals.

Male and female animals from all the treated dose groups exhibited comparable body weight gain with that of controls throughout the study period. Food consumption of control and treated animals was found to be comparable throughout the dosing period of 28 days and the recovery period of 14 days. In-life phase and cage side observations, conducted throughout the study period on control and the treated group animals did not reveal any abnormality. Hematological analysis conducted at the end of the dosing period on day 29 and at the end of recovery period on day 43, revealed no abnormalities attributable to the treatment.

Clinical chemistry profile of main group and recovery group animals did not reveal any significant results attributable to the treatment. Organ weight data of male and female sacrificed at the end of the dosing period and at the end of the recovery period was found to be comparable with that of respective controls. Gross pathological examination did not reveal any abnormality. Histopathological examination did not reveal any treatment related abnormalities

TABLE –I(a)
SUB-CHRONIC STUDY –RABBIT MALE & FEMALE
MORTALITY OF RABBIT EXPOSED TO TEST COMPOUND

S. No.	Days of observation	VC		TD		TD(I)		AD		HD	
		M	F	M	F	M	F	M	F	M	F
1	Base line	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
2	1	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
3	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
5	4	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4	5	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
7	6	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
8	7	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
9	8	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
10	9	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
11	10	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
12	11	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
13	12	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
14	13	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
15	14	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
16	15	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
17	16	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
18	17	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
19	18	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
20	19	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
21	20	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
22	21	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
23	22	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
24	23	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
25	24	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
26	25	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
27	26	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
28	27	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
29	28	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3

TABLE –I(b)
SUB-CHRONIC STUDY –RABBIT MALE & FEMALE
MORTALITY OF RABBIT EXPOSED TO TEST COMPOUND

S.No	Days of observation	SVC		SHD	
		M	F	M	F
1	Baseline	0/3	0/3	0/3	0/3
2	2	0/3	0/3	0/3	0/3
3	4	0/3	0/3	0/3	0/3
4	6	0/3	0/3	0/3	0/3
5	8	0/3	0/3	0/3	0/3
4	10	0/3	0/3	0/3	0/3
7	12	0/3	0/3	0/3	0/3
8	14	0/3	0/3	0/3	0/3
9	16	0/3	0/3	0/3	0/3
10	18	0/3	0/3	0/3	0/3
11	20	0/3	0/3	0/3	0/3
12	22	0/3	0/3	0/3	0/3
13	24	0/3	0/3	0/3	0/3
14	26	0/3	0/3	0/3	0/3

15	28	0/3	0/3	0/3	0/3
16	30	0/3	0/3	0/3	0/3
17	31	0/3	0/3	0/3	0/3
18	32	0/3	0/3	0/3	0/3
19	33	0/3	0/3	0/3	0/3
20	34	0/3	0/3	0/3	0/3
21	35	0/3	0/3	0/3	0/3
22	36	0/3	0/3	0/3	0/3
23	37	0/3	0/3	0/3	0/3
24	38	0/3	0/3	0/3	0/3
25	39	0/3	0/3	0/3	0/3
26	40	0/3	0/3	0/3	0/3
27	41	0/3	0/3	0/3	0/3
28	42	0/3	0/3	0/3	0/3
29	43	0/3	0/3	0/3	0/3

TABLE – II(a)
BODY WEIGHT - (kg) MALE

Groups	**Base line**	**3st day**	**7rd day**	**11th day**	**14th day**	**18th day**	**22nd day**	**27th day**
VC	1.37± 0.020	1.42± 0.043	1.47± 0.02	1.53± 0.06	1.58± 0.05	1.63± 0.02	1.69± 0.02	1.74± 0.04
TD	1.40± 0.035	1.429± 0.09	1.44± 0.160	1.45± 0.158	1.45± 0.18	1.48± 0.188	1.54± 0.180	1.59± 0.04
TD(I)	1.37± 0.05	1.39± 0.06	1.42± 0.126	1.43± 0.09	1.43± 0.092	1.453± 0.09	1.49± 0.08	1.57± 0.069
AD	1.54± 0.087	1.58± 0.03	1.603± 0.092	1.616± 0.092	1.627± 0.096	1.649± 0.099	1.68± 0.095	1.74± 0.09
HD	1.38± 0.08	1.40± 0.05	1.423± 0.136	1.473± 0.130	1.476± 0.129	1.508± 0.134	1.53± 0.1433	1.64± 0.088
SVC	1.39± 0.06	1.42± 0.072	1.48± 0.09	1.49± 0.09	1.52± 0.125	1.54± 0.127	1.57± 0.124	1.61± 0.125
SHD	1.56± 0.07	1.586± 0.045	1.61± 0.081	1.618± 0.089	1.625± 0.099	1.648± 0.101	1.687± 0.086	1.747± 0.089

TABLE II (b)
BODY WEIGHT - (kg) FEMALE

Groups	**Base line**	**3st day**	**7rd day**	**11th day**	**14th day**	**18th day**	**22nd day**	**27th day**
VC	1.35± 0.015	1.33± 0.025	1.37± 0.015	1.426± 0.029	1.422± 0.031	1.444± 0.028	1.438± 0.030	1.542± 0.043
TD	1.430± 0.158	1.413± 0.151	1.44± 0.110	1.43± 0.125	1.419± 0.140	1.441± 0.142	1.501± 0.163	1.548± 0.138
TD(I)	1.386± 0.125	1.356± 0.125	1.356± 0.102	1.381± 0.102	1.385± 0.096	1.452± 0.087	1.481± 0.092	1.608± 0.035
AD	1.38± 0.055	1.373± 0.066	1.346± 0.047	1.360± 0.057	1.362± 0.0536	1.424± 0.053	1.538± 0.051	1.568± 0.056
HD	1.426± 0.040	1.40± 0.0346	1.436± 0.080	1.493± 0.065	1.488± 0.067	1.525± 0.075	1.554± 0.078	1.645± 0.078

SVC	1.343± 0.040	1.356± 0.035	1.413± 0.035	1.41± 0.055	1.456± 0.011	1.503± 0.028	1.543± 0.025	1.593± 0.051
SHD	1.433± 0.094	1.396± 0.090	1.44± 0.104	1.428± 0.086	1.438± 0.075	1.484± 0.053	1.510± 0.066	1.598± 0.052

Values are expressed as Mean ± SD

TABLE – III (a)
FOOD INTAKE (gm) MALE

Groups	**Base line**	**3st day**	**7rd day**	**11th day**	**14th day**	**18th day**	**22nd day**	**27th day**
VC	46.6± 4.36	52.1± 4.3	56.86± 4.21	61.43± 4.63	67.06± 5.26	72.33± 5.65	75.93± 5.60	81.33± 4.05
TD	43.8± 5.15	49.8± 4.44	54.5± 3.91	60.16± 4.11	64.96± 3.70	70.1± 4.47	75.3± 4.15	80.5± 3.14
TD(I)	44.4± 3.80	48.4± 4.63	53.3± 4.14	58.7± 3.50	63.96± 3.47	68.5± 3.19	74.03± 3.42	78.46± 2.74
AD	46.3± 5.82	48.4± 4.63	53.3± 4.14	58.76± 3.50	63.6± 3.47	68.56± 3.19	74.03± 3.42	78.46± 2.74
HD	44.73± 2.75	49.2± 2.85	54.9± 3.20	60± 3.34	64.9± 2.90	69.76± 1.76	74± 2.77	78.43± 2.65
SVC	46.8± 3.3	51.9± 3.43	57.1± 3.08	61.3± 4.25	66.2± 3.55	71.2± 3.63	76.53± 2.87	81.23± 2.81
SHD	48.56± 3.60	53.2± 4.66	57.2± 5.72	62.2± 5.25	67.2± 5.65	71.53± 5.10	76± 4.15	80.2± 2.56

TABLE – III (b)
FOOD INTAKE (gm) FEMALE

Groups	**Base line**	**3st day**	**7rd day**	**11th day**	**14th day**	**18th day**	**22nd day**	**27th day**
VC	40± 3.55	43.93± 1.60	48.16± 1.51	53± 1.82	57.53± 2.61	61.6± 3.24	65.6± 3.3	68.7± 2.85
TD	39.23± 0.55	43.56± 1.33	47.9± 1.15	51.96± 1.68	56.8± 0.98	61.3± 1.45	65.63± 1.59	69.4± 1.04
TD(I)	37.7± 1.212	41± 0.55	44.86± 0.83	49.2± 0.5	56.86± 1.25	58.13± 1.75	62.53± 1.75	66.63± 2.35
AD	40.56± 0.85	45.26± 0.89	50.43± 1.19	55.2± 0.95	59.83± 0.95	65.13± 0.95	68.76± 1.73	72.26± 1.85
HD	39.9± 1.96	44.7± 1.82	49.06± 1.85	53.6± 1.00	58.2± 0.77	62.7± 0.17	67.06± 0.66	71.03± 1.26
SVC	41.16± 2.2	44.86± 2.34	49.16± 2.09	52.86± 2.05	56.9± 2.35	61.3± 1.91	65.86± 2.00	69.63± 0.86
SHD	40.86± 1.15	44.6± 1.05	48.73± 0.15	52.9± 1.49	58.2± 1.55	63.26± 1.50	67.33± 1.95	70.86± 1.67

Values are expressed as Mean ± SD

TABLE-IV (a)
HEMATOLOGY PARAMETERS - MALE

Groups	**VC**		**TD**		**TD(I)**		**AD**		**HD**	
Days (Post exposure)	0	28	0	28	0	28	0	28	0	28
Parameters										
WBC X 10^6/µL	8.5± 1.58	9.53± 0.75	9.03± 0.60	9.06± 1.20	9.1± 2.64	10.13± 1.15	8.1± 1.38	9.6± 2.52	8.1± 3.04	9.26± 2.08
RBC X 10^3/µL	5.15± 0.33	5.74± 0.58	5.22± 0.66	5.53± 0.20	4.94± 0.73	5.58± 0.27	4.92± 0.47	5.26± 0.78	4.4± 0.19	4.94± 0.16
Hgb g/dL	11.06± 1.05	12.93± 0.55	12.03± 2.10	13.7± 0.79	12.03± 1.70	13.53± 0.94	12.4± 0.88	13.16± 1.25	11.6± 1.10	12.66± 0.75
Hct %	39.66± 2.28	43.1± 3.99	43.93± 4.02	46.4± 1.11	39.5± 1.11	44.13± 2.20	41.06± 5.04	42.33± 3.95	39.2± 1.96	41.9± 1.77
MCV fL	77± 0.79	76.83± 2.75	83.3± 4.95	83.9± 3.35	81.3± 7.32	82.73± 8.54	82.3± 4.2	80.96± 7.24	84.9± 6.23	79.83± 6.61
MCH Pg	20.93± 1.44	22.06± 2.25	22.56± 2.05	24.7± 1.32	24.2± 2.58	24.56± 2.70	24.36± 1.61	25.2± 2.58	24.63± 1	25.6± 0.65
MCHC g/dL	27.13± 1.79	28.46± 2.20	27.1± 2.21	29.5± 0.96	29.03± 1.62	30.06± 1.74	29.4± 3.2	31.03± 0.46	28.4± 2.44	30.13± 1.19
Plt X10^3/µL	4.11± 2.04	4.44 ± 0.41	5.05± 3.32	4.67± 2.41	5.04± 1.24	5.37± 0.53	6.66± 0.42	6.38± 0.84	4.55± 1.34	4.74± 0.90

Values are expressed as Mean ± SD

TABLE-IV (a) continued …….

Groups	**SVC**		**SHD**	
Days (Post exposure)	0	28	0	28
Parameters				
WBC X 10^6/µL	9.16± 1.80	9.83± 1.40	6.56± 0.61	7.6± 0.91
RBC X 10^3/µL	5.73± 0.41	5.20± 0.22	4.46± 0.1	4.91± 0.28
Hgb g/dL	13.8± 0.75	13± 0.36	12.7± 0.4	12.86± 0.64
Hct %	47.33± 1.22	40.63± 1.37	40.06± 2.05	41.33± 2.49
MCV fL	82.4± 7.13	84.96± 3.06	86.8± 1.67	70.6± 7.92
MCH Pg	24.16± 2.85	24.7± 1.27	26.36± 1.20	23.06± 1.36
MCHC g/dL	29.53± 1.72	31.5± 1.47	30.06± 1.66	27.4± 2.33
Plt X10^3/µL	3.96± 1.34	4.60± 0.35	6.76± 1.44	5.05± 0.99

Values are expressed as Mean ± SD

TABLE - IV (b)
HEMATOLOGY PARAMETERS – FEMALE

Groups	**VC**		**TD**		**TD(I)**		**AD**		**HD**	
Days (Post exposure)	0	28	0	28	0	28	0	28	0	28
Parameters										
WBC X 10^6/µL	7.63± 0.66	9.06± 1.40	9.66± 0.75	10.13± 1.23	7.9± 1.34	9.86± 2.35	7.63± 1.12	7.96± 1.66	9.66± 3.15	9.36± 2.63
RBC X 10^3/µL	4.99± 0.52	5.67± 0.62	5.07± 0.23	5.31± 0.50	5.18± 0.50	4.96± 0.74	5.22± 0.97	5.79± 0.28	6.36± 2.32	5.23± 0.26
Hgb g/dL	12.96± 10.6	14.8± 0.55	12.33± 1.78	14.26± 0.85	14.8± 0.65	13.6± 1.8	14.63± 3.4	14.66± 0.98	13.1± 1.87	14.23± 0.90
Hct %	39.9± 3.85	45.86± 0.77	38.5± 6.61	46.13± 1.73	46.53± 1.10	43.26± 6.05	46.2± 4.75	46.2± 1.4	42.9± 4.2	45.73± 1.90
MCV fL	80.6± 6.71	87.8± 1.75	75.36± 10.6	87.2± 5.10	80.3± 3.49	86.87± 1.79	71.9± 8.72	79.76± 2.80	74.56± 13.97	87.5± 2.77
MCH Pg	25.8± 1.80	26.9± 1.24	25.33± 2.08	26.9± 0.96	25.63± 1.76	25.93± 2.51	25.03± 3.71	25.26± 1.23	23.03± 3.72	27.16± 1.15
MCHC g/dL	31.73± 1.51	32.03± 0.50	33.73± 3.06	31.03± 1.0	30.86± 0.68	29.63± 2.02	31.1± 1.05	31.93± 1.05	31.03± 1.04	31.9± 1.21
Plt X10^3/µL	5.50± 1.38	6.12± 0.49	7.28± 3.23	6.36± 1.14	4.82± 0.61	4.93± 1.16	4.59± 1.65	4.81± 1.20	3.94± 1.96	6.16± 0.79

Values are expressed as Mean ± SD

TABLE IV(b) continued ……

Groups	**SVC**		**SHD**	
Days (Post exposure)	0	28	0	28
Parameters				
WBC X 10^6/µL	10.03± 0.76	9.6± 0.7	7.06± 1.41	8.43± 2.07
RBC X 10^3/µL	5.42± 0.50	5.76± 0.47	5.14± 0.27	4.16± 0.98
Hgb g/dL	14.53± 0.83	13.83± 0.63	13.8± 0.43	12.93± 2.19
Hct %	46.1± 1.82	45.6± 1.24	43.4± 0.6	38.80± 4.97
MCV fL	83.7± 4.37	83.4± 6.13	86.6± 1	71.16± 9.58
MCH Pg	25.03± 0.51	25.76± 2.37	27± 0.98	24.96± 2.82
MCHC g/dL	31±0.78	31.53± 1.77	30.93± 0.32	29.3± 2.20
Plt X10^3/µL	5.14± 0.96	5.11± 0.13	4.94± 0.74	4.59± 0.77

Values are expressed as Mean± SD

TABLE –V (a)
BIOCHEMICAL PARAMETERS – MALE

Groups	**VC**		**TD**		**TD(I)**		**AD**		**HD**	
Days (Post exposure)	0	28	0	28	0	28	0	28	0	28
Parameters										
Glucose mg/dl	99.3± 2.3	83± 7.93	113± 12.2	104± 22.11	96.3± 17.6	79± 12.12	92.6± 18.7	105.6± 19.55	99± 9.64	92.6± 22.5
Creatinine mg/dl	0.7± 0.2	1± 0.2	0.9± 0.3	1.3± 0.26	0.86± 0.25	0.93± 0.15	0.96± 0.15	1.23± 0.513	0.8± 0.2	1.6± 0.26
SGPT IU/L	30± 8.8	28.33± 7.67	25.3± 5.6	32.66± 16.2	36± 10.5	26± 10.53	24± 6.2	21.6± 11.5	31± 5.29	39± 4.35

SGOT IU/L	33± 10.8	36± 6.55	33.6± 4.1	27± 11.35	37.3± 7.0	35.3± 6.65	31± 2.6	23.6± 6.65	37± 2.64	29.3± 3.05
Total protein gm/ dl	6.2± 0.3	6.83± 0.56	6.7± 0.3	7.5± 0.3	7.3± 0.58	6.9± 0.2	6.8± 0.3	7.23± 0.321	6.2± 0.3	7.96± 0.15
Total bilurubin mg/dl	0.21± 0.02	0.22± 0.02	0.26± 0.02	0.18± 0.03	0.22± 0.025	0.13± 0.04	0.2± 3.3	0.2± 0.03	0.25± 0.04	0.23± 0.07
BUN mg/dl	27.6±8.0	30.6± 4.04	28.3± 7.0	34± 4.35	45.3± 10.0	23± 5.29	27± 6.9	32.6± 2.85	26.6± 10.7	30± 2.64
Cholesterol mg/dl	98.6± 26.4	78.6± 8.5	90.3± 42.2	81± 28.5	143.3± 50.3	125.3± 21.73	115.3± 14.2	68.6± 19.7	91.6± 11.8	56.6± 18.03
ALP IU/L	135± 5.56	237.6± 49.5	128.6± 14.2	215± 76.2	135.3± 10.1	281± 81.1	135.3±6.5	276± 18.5	151.3± 10.9	286.3± 93.02
Sodium mmol/L	143± 1.7	139.3± 2.51	136± 4	143.3± 3.21	142.3± 7.7	137.3± 3.21	139± 3	141.6± 2.51	137.6± 3.7	143.3± 3.21
Potassium mmol/L	4.7± 1.1	4.1± 0.36	5.1± 0.25	4.6± 0.45	4± 0.36	4.3± 0.64	4.7± 0.26	4.6± 0.36	5.6± 0.4	4.13± 0.5
Chloride mmol/L	100.3± 1.5	101.3± 4.04	103.3± 4.0	100.6± 4.61	101.6± 3.51	97.6± 5.13	98.6± 2.08	106± 3.60	96.6± 1.52	82.66± 31.81

Values are expressed as Mean ± SD

TABLE V(a) continued ……

Groups	**SVC**		**SHD**	
Days (Post exposure)	0	28	0	28
Parameters				
Glucose mg/dl	91.3± 13.2	85.6± 11.93	67.6± 11.0	65.3± 6.02
Creatinine mg/dl	0.83± 0.32	0.9± 0.45	0.8± 0.26	0.6± 0.25
SGPT IU/L	33± 7.5	32.33± 8.02	32± 3.46	35.66± 6.65
SGOT IU/L	36± 8.5	23.6± 4.50	29± 4.58	43.3± 6.02
Total protein gm/dl	6.4± 0.6	7.06± 0.90	7.43± 0.8	6.2± 0.45
Total bilurubin mg/dl	0.22± 0.02	0.19± 0.02	0.21± 0.01	0.14± 0.03
BUN mg/dl	38.3± 9.5	22.6± 4.06	35± 7.93	26.3± 11.15
Cholesterol mg/dl	121.6± 10.4	84± 10.5	100± 10	68.66± 16.5
ALP IU/L	128± 19.6	222± 56	153± 7	130.3± 54.6
Sodium mmol/L	146± 6.2	141.3± 2.51	143± 8.18	142± 4
Potassium mmol/L	4.0± 0.9	4.3± 0.45	4.56± 0.97	3.63± 0.45
Chloride mmol/L	102± 4.5	100± 4	101.6± 4.72	97.6± 2.51

Values are expressed as Mean ± SD

TABLE- V (b)
BIOCHEMICAL PARAMETERS – FEMALE

Groups	**VC**		**TD**		**TD(I)**		**AD**		**HD**	
Days (Post exposure)	0	28	0	28	0	28	0	28	0	28
Parameters										
Glucose mg/dl	107.3 ±12.8	92.3± 14.2	103± 5.5	100.3± 7.09	83± 15.5	73± 14.52	92.3± 23.7	86.3± 6.65	73.67 ± 11.06	91± 11.35
Creatinine mg/dl	0.9± 0.1	1.33± 0.25	0.96± 0.25	0.96± 0.2	0.86± 0.152	0.73± 0.25	1.3± 0.3	1.6± 0.51	0.9± 0.2	1.4± 0.608
SGPT IU/L	35.6± 6.5	29.3± 4.16	36± 3.6	33± 9.84	36.3± 10.4	21.6± 3.5	48.6± 14.8	37± 18.2	35.66 ±6.50	38.66± 6.65
SGOT IU/L	31.3± 5.1	36.3± 4.04	28.3± 8.5	45± 18.3	35.3± 10.5	26.6± 11.7	27.6± 10.5	34.6± 11.3	28.33 ±6.02	32± 16.09
Total protein gm/dl	6.8± 0.2	7.43± 0.55	6.5± 1.0	7.26± 6.2	7.3± 1.0	7.33± 0.6	6.2± 0.3	8.13± 1.1	6.2± 0.4	7.5± 0.81
Total bilurubin mg/dl	0.26± 0.02	0.26± 0.05	0.25± 0.04	0.19± 0.02	0.22± 0.02	0.2± 0.02	0.26± 0.02	0.26± 0.01	0.28± 0.02	0.17± 0.05
BUN mg/dl	32.3± 3.5	32.6± 3.5	29.3± 8.5	33.6± 9.07	29.3± 5.85	28.6± 4.5	26.3± 6.4	28.6± 6.4	21± 3.6	33.3± 6.65
Cholesterol mg/dl	105± 18	141.3± 7.5	109± 10.5	65.33± 12.6	143.3± 15.2	96± 6.0	120.3 ± 25.1	96.3± 18	100± 13.1	87.3± 40.2
ALP IU/L	126.3 ± 8.08	398.6± 64	144.3± 9.7	291.3± 41	145.3± 4.7	257± 76	127.3 ± 9.6	256± 18.5	138± 21.1	196.3± 65.2
Sodium mmol/L	136± 1	138.3± 4.93	142.3± 2.5	138.3± 2.0	145.6± 10.9	141± 3	141.6 ± 2.5	142.3± 4.7	140.6 ± 3.5	141± 1
Potassium mmol/L	4.3± 0.7	4.36± 0.4	5.8± 0.36	4.3± 0.75	4.4± 0.62	4.3± 0.46	5.5± 0.55	4.6± 0.64	4.4± 0.3	3.9± 0.43
Chloride mmol/L	101± 2.08	98.3± 5.1	102.3± 6.65	98.6± 2.3	101.6± 3.05	103.5± 3.5	99.3± 2.51	97.6± 6.0	101.6 ± 2.51	106± 2.6

Values are expressed as Mean ± SD

TABLE V(b) continued ……..

Groups	**SVC**		**SHD**	
Days (Post exposure)	0	28	0	28
Parameters				
Glucose mg/dl	85.3± 11.3	81± 19	82.66± 17.21	71.66± 10.01
Creatinine mg/dl	1.0± 0.15	1± 0.3	1.1± 0.264	1.06± 0.351
SGPT IU/L	35.6± 6.5	24.3± 4.72	37± 7.54	28.66± 9.50
SGOT IU/L	34.6± 12.8	28.3± 6.50	38.33± 10.69	30± 11.53
Total protein gm/dl	7.1± 0.9	6.86± 1.12	7.3± 1.1	6.4± 0.62
Total bilurubin mg/dl	0.24± 0.04	0.19± 0.02	0.25± 0.04	0.20± 0.05
BUN mg/dl	42± 17.7	26.3± 4.5	37± 1.3	26± 6
Cholesterol mg/dl	116.6± 20.8	134.6± 45.5	110± 36	63± 16.0
ALP IU/L	135± 19.97	295± 145	148.6± 14.22	146± 66.7
Sodium mmol/L	145± 7.5	140± 5.56	139.3± 4.5	139± 5.5
Potassium mmol/L	3.7± 0.56	4.6± 0.6	3.7± 1.0	40.8± 0.60
Chloride mmol/L	100.6± 2.0	97.6± 3.5	102± 2	94± 2

Values are expressed as Mean ± SD

TABLE – VI(a)
URINE EXAMINATION - MALE

S. No	Parameters	DAY		VC	TD	TD(I)	AD	HD	SVC	SHD
				(% of animals)						
1	Glucose	0^h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
		28^{th}		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
2	Bilirubin	0^h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
		28^{th}		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
3	Ketone	0^h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
		28^{th}		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
4	Specific gravity	0^h	1	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			1.005	33.6 (1)0	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3.0 (1)	0.00 (0)
			1.0100	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1.0200	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)
			1.02	0.00 01)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			1.03	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
		28^{th}	1	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			1.005	33.6 (1)0	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3 (1)	0.00 (0)
			1.0100	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1.0200	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)
			1.02	0.00 01)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
5	Blood	0^h	Negative	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
		28^h		0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
6	pH	0^h	6	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			6.5	33.6 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			7.0	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			7.5	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			8.5	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)

			6	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			6.5	33.6.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
		28th	7.0	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			7.5	33.3.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			8.5	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)
7	Protein	0h	30+	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			100++	33.6 (1)0	33.3.0 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3.0 (1)	0.00 (0)
			300++	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			Trace	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)
		28th	30+	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			100++	33.6 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			300++	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			Trace	33.3.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
8	Urobilinogen	0h	0.2	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)
			1	33.6 (1)0	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3 (1)	0.00 (0)
		28th	0.2	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)

Values are in percentage

TABLE- VI (b)
URINE EXAMINATION – FEMALE

S. No	Parameters	DAY		VC	TD	TD(I)	AD	HD	SVC	SHD
				(% of animals)						
1	Glucose	0h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
		28th		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
2	Bilirubin	0h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
		28th		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
	Ketone	0h	Negative	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)

3		28th		100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)	100.0 (3)
4	Specific gravity	0h	1	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			1.005	33.6 (1)0	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3 (1)	0.00 (0)
			1.0100	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1.0200	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)
			1.02	0.00 01)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			1.03	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
		28th	1	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			1.005	33.6 (1)	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3 (1)	0.00 (0)
			1.0100	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1.0200	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)
			1.02	0.00 01)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
5	Blood	0h	Negative	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
		28h		0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
6	pH	0h	6	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			6.5	33.6 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			7.0	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			7.5	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			8.5	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)
		28th	6	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			6.5	33.6 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			7.0	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			7.5	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			8.5	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)
7	Protein	0th	30+	33.6 (1)	66.6 (2)	0.00 (0)	66.6 (2)	33.3 (1)	66.6 (2)	0.00 (0)
			100++	33.6 (1)0	33.3 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3 (1)	0.00 (0)
			300++	33.6 (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			Trace	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)

		28th	30+	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
			100++	33.6 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
			300++	0.00 (0)	0.00 (0)	25.0 (1)	0.00 (0)	0.00 (0)	0.00 (0)	25.0 (1)
			Trace	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)
8	Urobilinogen	0h	0.2	33.3 (1)	100.0 (3)	100.0 (3)	100.0 (3)	33.3 (1)	100.0 (3)	100.0 (3)
			1	33.6. (1)0	33.3.0 (1)	0.00 (0)	0.00 (0)	33.3 (1)	33.3.0 (1)	0.00 (0)
		28th	0.2	33.6. (1)	0.00 (0)	66.6 (2)	33.3 (1)	33.3 (1)	0.00 (0)	66.6 (2)
			1	0.00 (0)	0.00 (0)	33.3 (1)	0.00 (0)	0.00 (0)	0.00 (0)	33.3 (1)

Values are in percentage

TABLE - VII(a)
ORGAN WEIGHTS (gm) - MALE

Groups	**VC**	**TD**	**TD(I)**	**AD**	**HD**	**SVC**	**SHD**
Days (Post exposure)	28	28	28	28	28	28	28
Parameters							
Heart	5± 1.11	5.53± 1.10	5.63± 0.75	5.8± 0.529	5.06± 0.46	5.43± 0.873	7.16± 0.25
Lung	10.16± 1.93	10.93± 0.41	10.96± 0.602	10.4± 1.44	9.66± 1.55	9.7± 0.75	10.23± 1.19
Liver	66.4± 7.30	72.16± 7.71	72.13± 8.05	63.43± 10.69	55.3± 6.58	64.8± 8.63	59.96± 4.55
Kidney Left & Right	13.76± 2.61	11.4± 1.21	10.9± 0.5	13.06± 1.8	12.8± 1.2	14.03± 1.70	12.9± 1.212
Brain	6.8±0.8	6± 0.346	5.86± 0.152	6.86±0 .23	6.4± 0.72	6.66± 0.50	6.4± 0.88
Spleen	1.3± 0.3	1.2± 0.346	1.13± 0.251	1.13± 0.30	1± 0.346	1.2± 0.2	1.2± 0.264

Values are expressed as Mean± SD

TABLE - VII(b)
ORGAN WEIGHTS (gm) - FEMALE

Groups	VC	TD	TD(I)	AD	HD	SVC	SHD
Days (Post exposure)	28	28	28	28	28	28	28
Parameters							
Heart	5.06± 0.230	4.8± 0.529	6.1± 0.4	7.6± 1.79	5.4± 0.721	5.33± 0.40	5.3± 0.4
Lung	12.13± 2.30	9.46± 0.23	9.4± 0.5	8.6± 0.871	8.8± 2.30	11.26± 0.70	10.76± 1.42
Liver	77.4± 2.48	56.1± 6.05	57.75± 3.32	66.42± 12.03	56.23± 14.83	75.7± 4.5	58.06± 14.17
Kidney Left & Right	13.1± 0.1	13.1± 1.97	12.83± 1.88	11.4± 1.24	13.4± 0.721	13.36± 0.76	13.23± 1.106
Brain	6.5± 0.7	6.8± 0.50	6.4± 0.62	6.4± 0.2	7.3± 0.64	6.6± 0.81	7.2± 0.56
Spleen	1.86± 0.41	1.06± 0.642	1.63± 0.152	1.2± 0.871	1.3± 0.577	1.23± 0.416	1.76± 0.30

Values are expressed as Mean ± SD

IV. CONCLUSION

In conclusion, no specific outcome of toxicological significance was noted with the repeated administration of recombinant Enfuvirtide as compared to the Vehicle control and Innovator's synthetic enfuvirtide.

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