

Chronic Orally Toxicity Study with Geranti Dry
Yeast-G (Geranti Bio-Ge Yeast)
in Rats and Beagle dogs

January 30, 2001

*Laboratory of Anatomy and Laboratory of Immunopharmacology,
Department of Veterinary Medicine,
Kang-Won National University, Korea*

< Report 1 >

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Chronic Toxicity of Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) Orally Administered to Rats for 10 Consecutive Months

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ABSTRACT: *The purpose of this study was to examine the chronic toxicity Sprague-Dawley (SD) rats treated orally Geranti Dry Yeast-G (Geranti Bio-Ge Yeast developed by GerantiPharm Ltd.) In chronic toxicity test, three groups (30 rats of both sex) were administered daily different dosages of Geranti Dry Yeast-G (Geranti Bio-Ge Yeast), 3,000mg/kg body wt/day (high dosage group), 300mg/kg body wt/day, 30mg/kg body wt/day and one group (control group, 10 rats of both sexes) were received by orally only water for 10 months according to the Regulation on Korea Food and Drug Administration (1998.4.29), respectively. There was no difference in body weight change, feed intake or water consumption among different dose groups. There was no alteration in relative organ weights by the administration of Geranti Dry Yeast-G (Geranti Bio-Ge Yeast). No death or abnormal clinical sign was observed through the dosing period. Between the groups orally administered Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) and the control group, there was no statistical significance in urinalysis, hematological tests or serum biochemical values. There were no gross findings at final sacrifice. There was no evidence of histopathological alteration mediated by chronic treatment with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast). These results suggest that no observable effect level (NOEL) of the test substance was considered to be more than 3,000mg/kg body wt/day in rats under the conditions employed in this study.*

Key Words: Chronic toxicity, Geranti Dry Yeast-G (Geranti Bio-Ge Yeast), SD rats

I . Introduction

Germanium is present in all living plant and animal matter in micro-trace quantities. Organic germanium compounds have been used therapeutically within research and clinical practices for almost three decades, yet germanium is not presently listed as a nutritional trace element. Its therapeutic attributes include immuno-enhancement, oxygen enrichment, free radical scavenging, analgesia and heavy metal detoxification. Toxicological studies document organic germanium's rapid absorption and elimination from the body, and its safety. Clinical trials and use in practices for more than three decades has demonstrated germanium's efficacy in treating a wide range of serious afflictions including cancer, arthritis and senile osteoporosis.

In 1987, the R&D Center of GerantiPharm Ltd. began to search for an efficient and economical way to provide the public with organic germanium. Five years later, Geranti Pharm Ltd. succeeded in biosynthesizing natural organic germanium (namely Biogermanium) using biotechnical microorganism and this process was patented internationally in countries such as Korea, Japan, and the United States. Geranti Dry Yeast-G(Geranti Bio-Ge Yeast), which was developed for the enhancement of safety has passed the acute oral toxicity test at US FDA reg. laboratory of Biological Test Center.

The purpose of this study was to examine the chronic toxicity in SD rats treated intragastrically Geranti Dry Yeast-G (Geranti Bio-Ge Yeast developed by GerantiPharm Ltd.).

II. MATERIALS AND METHODS

1. Animals

Eighty Sprague-Dawley rats, 40 male and 40 female, obtained from Charles River Japan were used in this study. The rats were approximately 4 week old when obtained. They were acclimated in environmentally controlled rooms (temperature: $23 \pm 2^\circ\text{C}$, relative humidity: $50 \pm 5\%$, air circulating frequency: 10-12 times/hr, artificial light: 150-200 Lux from 7 am to 7 pm, noise: < 50 db) in Animal Center for Pharmacologic Research in Kangwon National University for 10 days before initiation of Dry Yeast-G administration. Rats were housed in a polycarbonate cage (26cm \times 42cm \times 18cm). The number of rats in a cage was five or less. Regular lab chow (Samyang Co., Seoul) and tap water were provided *ad libitum*.

2. Test substance

Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) was supplied from Geranti Pharm Ltd. The test substance was prepared every week and stored in a refrigerator ($\leq 4^\circ\text{C}$) until use. The test substance was stirred and resuspended on a hot plate immediately prior to use. The volume of administration was adjusted to 20 ml/kg body weight.

3. Study design

Experiments were conducted according to "Guidelines for Toxicity Testing of Pharmaceuticals" (KFDA, 1998). For detailed experimental procedure "Standard Operating Procedures in Toxicology" (Inveresk Research International, 1979) was referred.

A total of 40 male and 40 female rats were used in this study. Rats of each sex were randomly assigned to 4 groups. The largest dose of the test substance administered to rats was 3,000mg/kg body wt/day. This preparation was used as the high dose followed by sequential dilution with water to 300mg, and 30mg, for the medium dose, and the low dose, respectively. Control animals were treated with an identical volume of water only. The high dose (3,000mg/kg body wt/day) of the test substance employed was equivalent to an anticipated clinical dose given to a man weighing 60 kg. The test substance was administered to a rat intragastrically using a curved blunt-ended metal cannula attached to a disposable syringe between 9:30 and 10:30 am every morning. Rats were treated with the test substance 7 days a week, for 10 consecutive months.

Rats were observed for abnormal clinical signs at least once a day for the whole period

of the test substance administration. Body weight of each rat, food and water intake by the cage, were measured twice in a week for the first one month and once in a week thereafter.

Urine was collected from each rat once in the final week of administration. The parameters determined in urinalysis included glucose, bilirubin, ketone body, specific gravity, occult blood, protein, urobilinogen, pH, nitrite, and white blood cell. After the administration period of 10 months blood was collected from abdominal aorta in rats under light ether anesthesia and used for hematology and serology measurements. For hematological measurements white blood cell(WBC), red blood cell(RBC), hematocrit, hemoglobin, platelet, mean corpuscular volume(MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), prothrombin time(PT), partial thromboplastin time(PTT), and differential leucocyte count were determined. The serum chemistry parameters included total protein, total bilirubin, glucose, alkaline phosphatase(ALP), total cholesterol, aspartate transaminase(AST), alanine transaminase (ALT), triglyceride(TG), blood urea nitrogen (BUN), and creatinine. After sacrifice by exsanguination all major organs and tissues were examined grossly and the weight was measured. Major organs and tissues including brain, liver, heart, kidney(R/L), lung, adrenal gland(R/L), spleen, testis(R/L), ovary(R/L) and bone marrow from femoral bone were fixed in 10% neutral buffered-formalin solution and processed for microscopic examination.

4. Statistical analysis

All results expressed as means SD were analyzed by one way ANOVA followed by *Dunnett's t-test*. For nonparametric urinalysis data, "Kruskal-Wallis" H test was used and differences between groups were determined by distribution-free multiple comparison test. Fisher's exact test was employed to analyze clinical signs, necropsy and histopathology findings.

III. RESULTS AND DISCUSSION

1. Mortality and clinical signs

There was no death among the rats used in this study during the observation period of 10 months (Table 6). Throughout the experimental period, there was no abnormal behavior or appearance associated with administration of the test substance among the animals regardless of sex and dose levels employed.

2. Body weight

The body weight of rats was monitored for 10 months (Fig. 1 and Fig. 2). There was no difference in mean body weight increase among the different dose groups of each sex throughout the experimental period.

3. Food and water consumption

There was no difference in food and water intake ratio among the different dose groups of each sex throughout the experimental period (data were not shown).

4. Urinalysis

The parameters determined in urinalysis did not demonstrate statistical differences among the groups except for the slight increase in pH level in the high dose group of both sexes (Table 1).

However, the changes were not considered to be related to the test substance.

5. Hematology

Hematological readings are shown in Table 2. There were no statistical differences in white blood cells, red blood cells, hemoglobin, hematocrit, platelet, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration among the different dose groups of each sex throughout the experimental period. Also there were no significant differences in differential count of white blood cells.

There were no significant differences in prothrombin time and partial thromboplastin time among the different dose groups of each sex throughout the experimental period (Table 4). All the differences observed are small and did not show any dose-dependency. Furthermore, all the values appeared to be in normal range.

6. Serum chemistry

Serum biochemical values are summarized in Table 3. The parameters determined in serum chemistry did not demonstrate statistical differences among the groups except for the alanine transaminase(ALT) and creatinine level. In the female rats small differences among the different dose groups included and a decrease in ALT activity in the Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) group. In contrast, there was a slight increase of creatinine in the Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) group. However, all the small differences in ALP and creatinine appeared to be inconsistent in terms of the dose administered of sex. All the values appeared to be in normal range.

7. Autopsy and organ weight

After the administration period of 10 months all animals were sacrificed, and major organs and tissues were examined grossly. No lesions were observed in the animals regardless of the dose of the test substance administered (Table 7). Data concerning relative organ weights are shown in Table 5. There were no other changes in the organ weight associated with administration of the Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) among the different dose groups.

8. Histopathology

Major organs and tissues in the control and the high dose groups were processed for microscopic histopathological examination (Table 7). It was observed in kidney tissue specimen that the glomerulus, the glomerular capsule, the eosinophilic proximal convoluted tubules lined by simple cuboidal epithelium showing brush border. The distal tubules in which nucleus located in the apical part of the cell and stained with bright were normal structures. Some swelling cells observed in medullary ray, however it was not estimated the germanium effects since the configuration of the cells was seen in the control and the experiment groups. In the control and the experimental groups, liver acinus showed the normal hepatocytes and the hepatic sinusoids. No inflammatory reaction in portal area and central vein are observed in both groups. The cardiac muscle cells were seen normal in size and arrangement in both the control and the experimental groups. The red pulp and the white pulp having germinal center and marginal zone were well established in both the control and the experimental groups. Also Macrophages containing the hemosiderin were observed in red pulp in both the control and the experimental groups. In the gastric wall of control group and experimental groups, epithelial cell, mucous neck cells, chief cell, eosinophilic parietal cells constitute the simple tubular glands. No pathologic finding as much inflammatory cell infiltration was observed. In conclusion, there was no evidence of histopathological alteration mediated by chronic treatment with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast).

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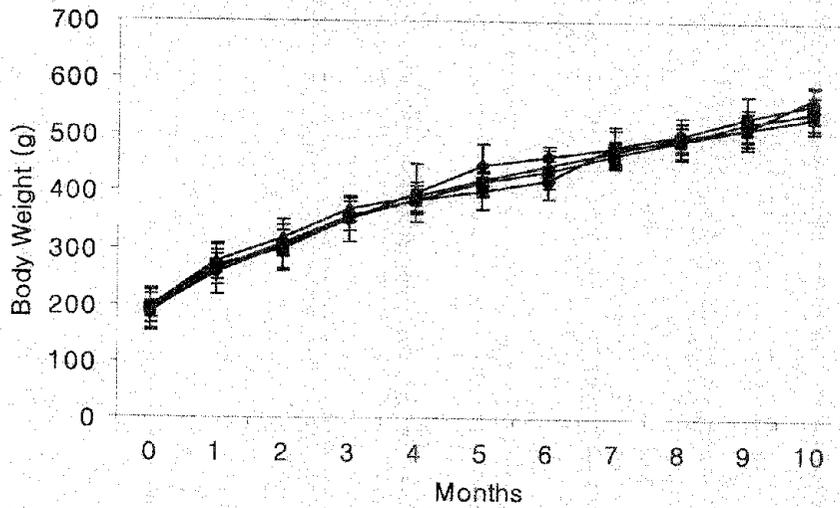


Fig 1. Mean body weight changes in male rats administered orally with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) for 10 months.

-♦- : Control, -■- : 30mg, -▲- : 300mg, -●- : 3,000mg

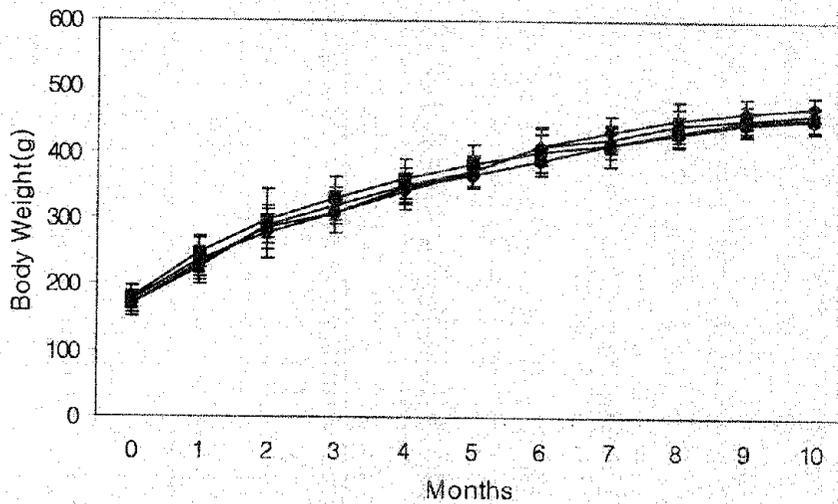


Fig 2. Mean body weight changes in female rats administered orally with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) for 10 months.

-♦- : Control, -■- : 30mg, -▲- : 300mg, -●- : 3,000mg

Table 2. Hematological values of rats treated with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) orally for 10 months

Parameters	Dose(No. of Rats)							
	Control		30mg		300mg		3,000mg	
	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)
WBC($\times 10^3/\mu\text{l}$)	9.46 \pm 0.51 ^{a)}	9.53 \pm 0.64	9.67 \pm 0.95	9.87 \pm 0.89	9.46 \pm 0.86	9.14 \pm 0.45	9.93 \pm 1.01	9.64 \pm 0.38
RBC($\times 10^6/\mu\text{l}$)	7.88 \pm 0.16	7.96 \pm 0.11	7.99 \pm 0.14	8.02 \pm 0.25	7.56 \pm 0.52	7.76 \pm 0.41	7.76 \pm 0.43	8.21 \pm 0.21
HGB(g/dl)	13.69 \pm 0.41	14.14 \pm 0.85	14.59 \pm 0.50	13.01 \pm 0.90	14.91 \pm 0.70	13.91 \pm 0.62	14.46 \pm 0.10	13.90 \pm 0.71
HCT(%)	40.21 \pm 2.14	41.00 \pm 3.41	42.21 \pm 0.76	41.90 \pm 1.67	43.51 \pm 2.34	40.91 \pm 2.67	43.25 \pm 1.30	42.35 \pm 1.76
PLT($\times 10^3/\mu\text{l}$)	1069.46 \pm 71.59	990.91 \pm 80.01	998.01 \pm 90.25	1041.66 \pm 90.10	1027.81 \pm 40.30	1029.86 \pm 71.61	999.46 \pm 69.21	1019.11 \pm 63.19
MCV(fl)	51.32 \pm 3.21	53.32 \pm 2.43	52.87 \pm 1.67	54.21 \pm 1.54	51.98 \pm 1.09	53.32 \pm 1.31	51.95 \pm 1.67	52.44 \pm 2.11
MCH(pg)	31.45 \pm 2.00	32.31 \pm 1.23	31.75 \pm 1.23	33.11 \pm 1.43	31.94 \pm 1.26	32.63 \pm 1.78	32.76 \pm 1.30	31.35 \pm 1.00
MCHC(g/dl)	33.24 \pm 3.25	31.34 \pm 1.76	32.46 \pm 2.36	32.90 \pm 2.15	31.50 \pm 2.49	33.01 \pm 1.06	31.45 \pm 1.99	32.01 \pm 2.34
Neutrophil(%)	21.02 \pm 3.21	18.85 \pm 1.78	17.33 \pm 2.07	18.99 \pm 2.99	16.26 \pm 2.10	19.75 \pm 2.30	18.06 \pm 2.09	16.81 \pm 1.02
Lymphocyte(%)	78.01 \pm 4.80	80.37 \pm 3.79	81.77 \pm 2.87	79.01 \pm 2.01	82.74 \pm 4.39	80.25 \pm 2.01	81.03 \pm 2.64	81.77 \pm 3.06
Monocyte(%)	0.97 \pm 0.26	0.78 \pm 0.27	0.90 \pm 0.16	0.20 \pm 0.01	1.00 \pm 0.98	0.00 \pm 0.00	0.91 \pm 0.39	1.42 \pm 0.25
Eosinophil(%)	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00
Basophil(%)	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00

^{a)} Values were expressed as mean \pm S.D. of 10 rats.; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; PLT, platelet; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration

Table 3. Serum biochemical values of rats per oral administration with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) for 10 months

Parameters	Dose(No. of Rats)							
	Control		30mg		300mg		3,000mg	
	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)
GLU(mg/dl)	119.20±10.99 ^{a)}	120.29±11.25	118.61±8.65	119.00±10.85	120.47±7.99	121.22±10.27	120.44±7.37	119.46±10.25
CHOL(mg/dl)	77.40±2.70	80.55±6.25	79.50±4.49	81.10±5.22	79.99±7.46	82.36±6.19	80.87±5.54	81.22±7.12
BUN(mg/dl)	23.16±2.14	22.22±1.15	21.91±1.22	23.08±2.66	23.90±1.72	23.95±2.26	22.26±2.19	23.90±3.71
TB(mg/dl)	0.33±0.22	0.30±0.22	0.38±0.11	0.35±0.16	0.40±0.19	0.32±0.32	0.29±0.09	0.31±0.21
AST(IU/l)	90.60±13.35	91.19±18.30	95.10±7.62	97.64±8.61	91.28±8.43	98.88±11.36	92.43±15.22	95.31±13.11
ALT(IU/l)	40.13±7.22	43.43±9.54	42.48±6.46	39.52±3.45	41.49±5.50	40.66±5.63	39.59±5.56	40.33±5.55
TG(mg/dl)	98.33±10.33	99.53±9.52	101.37±7.32	98.51±11.24	101.44±15.32	102.36±11.27	99.57±9.83	102.33±10.41
CREAT(mg/dl)	0.90±0.15	0.88±0.16	0.80±0.22	0.90±0.05	0.89±0.24	0.91±0.11	0.79±0.22	0.92±0.11
Albumin(g/dl)	4.30±0.99	3.95±0.24	4.22±0.74	4.16±0.53	4.02±0.13	4.11±0.30	3.99±0.68	4.18±0.72
Ca(mg/dl)	11.22±0.48	14.97±1.27	11.37±0.58	14.34±0.71	11.74±0.91	14.37±2.10	11.53±0.44	15.01±0.75
ALP(IU/l)	180.80±11.32	134.37±10.44	179.79±10.41	139.55±15.11	181.00±8.25	133.40±14.32	180.04±7.77	137.07±16.52
TP(g/dl)	6.87±0.16	6.48±0.77	6.30±0.83	6.60±0.15	6.86±0.57	6.88±0.12	6.55±0.46	6.90±0.43

^{a)} Values were expressed as mean ± S.D. of 10 rats.; GLU, glucose; CHOL, total cholesterol; BUN, blood urea nitrogen; TB, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; TG, triglyceride; CREAT, creatinine; CA, calcium; ALP, alkaline phosphatase; TP, total protein.

Table 4. Prothrombin time and partial thromboplastin time in rats treated with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) orally for 10 months

Parameters	Dose(No. of rats)							
	Control		30mg		300mg		3,000mg	
	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)
PT	17.40±2.09 ^{a)}	17.00±2.40	16.50±2.35	17.75±1.90	16.50±2.75	17.20±2.50	17.05±3.10	17.20±2.35
PTT	30.00±5.99	31.20±7.10	28.15±8.00	29.90±6.75	28.75±6.00	30.55±6.75	30.05±6.00	29.50±7.00

^{a)} Values were expressed as mean ± S.D. of 10 rats; PT, prothrombin time; PTT, partial thromboplastin time.

Table 5. Relative organ weights of rats treated with Geranti Dry Yeast-G (Geranti Bio-Ge Yeast) orally for 10 months

Unit: (%)

Parameters	Dose(No. of Rats)							
	Control		30mg		300mg		3,000mg	
	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)	♂ (10)	♀ (10)
Heart	0.45±0.04 ^{a)}	0.44±0.04	0.47±0.03	0.48±0.03	0.45±0.03	0.45±0.02	0.44±0.03	0.44±0.04
Liver	3.24±0.11	3.34±0.15	3.45±0.44	3.26±0.31	3.25±0.21	3.16±0.11	3.27±0.16	3.30±0.20
Spleen	0.30±0.03	0.29±0.03	0.30±0.02	0.30±0.02	0.30±0.01	0.32±0.02	0.29±0.01	0.30±0.01
Brain	0.86±0.02	1.02±0.04	0.90±0.11	1.01±0.03	0.85±0.02	0.99±0.04	0.88±0.03	1.02±0.05
Adrenal gland	Left	0.01±0.00	0.01±0.00	0.02±0.00	0.02±0.00	0.01±0.00	0.02±0.00	0.01±0.00
	Right	0.01±0.00	0.02±0.00	0.01±0.00	0.01±0.00	0.02±0.00	0.02±0.00	0.01±0.00
Thymus gland		0.30±0.05	0.31±0.04	0.30±0.03	0.29±0.03	0.31±0.02	0.30±0.03	0.29±0.02
Salivary gland	Left	0.11±0.02	0.12±0.01	0.12±0.02	0.10±0.02	0.11±0.01	0.11±0.02	0.11±0.01
	Right	0.13±0.01	0.12±0.01	0.12±0.02	0.12±0.01	0.12±0.02	0.12±0.01	0.12±0.01
Lung		0.65±0.05	0.64±0.04	0.67±0.07	0.65±0.05	0.64±0.05	0.66±0.05	0.63±0.04
Kidney	Left	0.40±0.03	0.41±0.03	0.39±0.02	0.40±0.02	0.41±0.03	0.40±0.02	0.40±0.03
	Right	0.39±0.02	0.39±0.03	0.40±0.03	0.41±0.03	0.40±0.02	0.40±0.03	0.40±0.02
Testis/Ovary	Left	0.66±0.05	0.03±0.01	0.65±0.02	0.04±0.01	0.64±0.04	0.04±0.01	0.65±0.03
	Right	0.65±0.04	0.03±0.01	0.64±0.02	0.03±0.01	0.61±0.05	0.04±0.01	0.63±0.02

^{a)} Values were expressed as mean ± S.D. of 10 rats.

Table 7. Autopsy findings of male and female rats after oral administration of Geranti Dry Yeast-G (Geranti Bio-Ge Yeast)

		Dose (mg)							
		0		30		300		3,000	
Fate		tk*	fd	tk	fd	tk	fd	tk	fd
No. of animals	Male	10	0	10	0	10	0	10	0
	Female	10	0	10	0	10	0	10	0
Male	NAD	10		10		10		10	
Female	NAD	10		10		10		10	

* tk: Terminal killed, fd: Found dead, NAD: No abnormality detected.