

FINAL REPORT

**A 4-Week Repeated Inhalation Toxicity of Ion
generating module HADES in Sprague-Dawley
Rats**

Study Number: 14-RR-171N

Sponsor: IM Healthcare Co., Ltd.

Nonclinical Research Institute, Chemon Inc.



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Translation Verification Statement

This report is a translation of original Korean Final Report issued on Jul 22, 2014.

Hereby, I certify that the contents are accurately translated.

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Study Overview

Title	A 4-Week Repeated Inhalation Toxicity of Ion generating module HADES in Sprague-Dawley Rats	
Objectives	The objective of this study was to evaluate the toxicity of the test article ion generating module HADES when administered daily by inhalation to Sprague-Dawley rats for a period of 4 weeks using the acryl box installed in the ion generating module HADES.	
Regulatory guidelines	This study was performed based on consultation with the sponsor.	
Sponsor	IM Healthcare Co., Ltd. #1-130, Medical Industry Technocenter, 42-10, Taejanggongdan-gil, Wonju-si, Gangwon-do, 220-962, Republic of Korea. +82-70-4262-2122 (TEL), +82-31-8605-4030 (FAX). Managing Director: Inje Yi	
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Schedules	Mar 27, 2014 Apr 04, 2014 Apr 11, 2014 May 08, 2014 May 09, 2014 Jun 13, 2014 Jul 15, 2014 Jul 22, 2014	Approval of protocol (study initiation) Animal acquisition (experimental initiation) Initiation of inhalation Completion of inhalation Blood sampling, Necropsy and Organ fixation Completion of histopathologic examination (Experimental completion) Submission of draft report Submission of final report (study completion)

Contributing Scientists	Animal care:	Min-Hyeok Choi
	Storage / Preparation of the test article:	Ji-Hoon Kim
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Archives Protocol, final report, raw data and other relevant evidential documents will be retained in the Archives of Nonclinical Research Institute, ChemOn Inc., at least three years after the completion of the study. Further storage of above materials shall be consulted with the Sponsor.

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Summary

This study was performed to evaluate the inhalation toxicity by ion generating module when when exposed by ion generating module HADES for 4 weeks in Sprague-Dawley rats.

The groups were consisted of vehicle control group (G1) and ion generating module HADES inhalation group (G2). Each group comprised 6 animals per sex.

Observation and examination items were as follows, and the results of the treatment groups were compared with those of the vehicle control group: clinical signs, animal death, body weight changes, food intake, urinalysis, organ weight, hematology, clinical biochemistry and histopathologic examination.

The results are summarized as follows.

1. Results of clinical signs and animal death, the ion generating module HADES inhalation group was not observed in abnormal sign or death animals.
2. There was not observed in body weight changes by test article.
3. Results of food intake, the ion generating module HADES inhalation group was not different from vehicle control group.
4. Results of organ weights, the all organ were not observed in difference between ion generating module HADES inhalation group and vehicle control group.
5. Results of urinalysis, the ion generating module HADES inhalation group was not different from vehicle control group.
6. Results of hematology, the ion generating module HADES inhalation group was not different from vehicle control group.
7. Results of clinical biochemistry, the ion generating module HADES inhalation group was not different from vehicle control group.
8. Results of histopathologic examination, the ion generating module HADES inhalation group was not different from vehicle control group.

Based on the results, the test article ion generating module HADES was not different from vehicle control group in all measurement items when administered daily by inhalation to Sprague-Dawley rats for 28 days. Therefore, the ion generating module HADES was determined that there was no difference for toxicity.

Materials and Methods

1. Test article

1) Test article

Name:	HADES
Code No. in test facility:	C-1600
Lot No.:	ION-HADES
Date of receipt:	Mar 18, 2014
Amount:	1 ea
Appearance:	Not supplied
Purity:	Not supplied
Expiration date:	Not supplied
Storage condition:	Room temperature
Supplier:	IM Healthcare co., Ltd.

2. Preparation of dose formulation and analysis

1) Preparation of dose formulation

Test article provided by sponsor were directly used acryl box to attach it because of ion generating module.

3. Test system and husbandry

1) Test system

(1) Animal information

Species and strain	Specific pathogen free (SPF) rats, NTacSam:SD		
Breeder / Supplier	Samtako Co. Ltd (105, Seorang-ro, Osan-si, Gyeonggi-do, Korea)		
Justification of selection	The SD rat used in this experiment is commonly used experimental animal in the efficacy/pharmacology. In addition, as sufficient raw data have been accumulated, those data are available in interpretation and evaluation of test results.		
Sex		Male	Female
Number of animals	At receipt	15	15
	At dose	12	12
Age of animals	At receipt	5	5
	At dose	6	6
Body weight ranges	At receipt	132.93 – 146.44 g	116.60 – 127.13 g
	At dose	188.10 – 211.81 g	148.18 – 169.65 g
Disposition of remnant animals	The remainders were euthanized.		

(2) Quarantine and acclimation

The animals were acclimated under the laboratory conditions for 7 days after receipt of the animals. General clinical observations were made once a day and only healthy animals were selected for the further experiment. According to the certificate provided by the supplier, there were no factors that could have an effect on the study.

(3) Identification

Animals were individually distinguished by tail marking using a red permanent marker pen during the acclimatization period. And identification method was used a black permanent marker pen during administration and observation periods. Cages were identified by color-coded animal ID cards. Serial numbers were given to the cage racks. A log sheet was posted up on the entrance of the animal room to identify this study.

(4) Animal experimentation ethics

This study was performed in accordance with the Animal Experimentation Policy of Gyeonggi Bio Research Center. (Serial number: 2014-03-0007)

2) Animal husbandry

(1) Environmental conditions and monitoring

This study was performed within the animal facility area No. 2 of Kyunggi bio Center and the animals were housed in a room that was maintained at a temperature of 23 ± 3 °C and a relative humidity of 55 ± 15 %, with artificial lighting from 08:00 to 20:00, 150-300 Lux of luminous intensity and 10~20 air changes per hour. There were no deviations that could affect this study.

(2) Diet, bedding, water, and contaminant monitoring

Animals were offered irradiation-sterilized pellet diet for lab animal (Teklad certified irradiated global 18 % protein rodent diet, 2918C, Laboratories Inc., USA) purchased from Dooyeol Biotech (107-ho, Sungbo Plaza, Yangjae-dong, Seocho-gu, Seoul, Korea) *ad libitum*. According to the certificates on diet component and contaminant supplied by diet provider, there was no factor that could affect results of this study.

Examination of water was performed by an authorized Gyeonggido Institute of Health & Environment. (324-1, Pajang-dong, Jangan-gu, Suwon-si, Gyeonggi-do, Korea) and the quality satisfied the standards for the drinking water.

(3) Cages and housing density

No more than 3 animals were housed in a polycarbonate cage (W 235 × L 380 × H 175 mm) during the quarantine, acclimation, administration and observation period.

(4) Renewal of housing materials

The cages with bedding and water bottles were replaced with clean ones once a week.

4. Group identification, selection of dose, grouping and administration

1) Group identification

Group	Sex	No. of animal	Animal ID	Test article
G1	M/F	6/6	1-6/13-18	-
G2	M/F	6/6	7-12/19-24	HADES

2) Selection of dose

The selection dose was not decided because of the test article was ion generating module.

3) Grouping

Healthy animals were selected after the acclimation period. They were weighed and then, referring to the rank of body weight, allocated randomly to groups as shown in the table of “group identification”.

4) Administration

Route and justification	Inhalation has been selected since human exposure will occur via this route.
Frequency and duration	24 hours, 7 times for week, for 4 weeks.
Dose volume	The continuous inhalation 24 hours, regardless of the weight. However, the exchange of the cage, and stops the intake feed intake and body weight measured at the time.
Method	We continue to inhalation the state put a cage for rats in the 1 x 1 x 0.7 m acryl box exposed to the ion.

5. Observations and examinations

1) Clinical signs

Each animal was observed daily for clinical signs. If there is any sign, the date and severity of the symptom was recorded individually. During the administration and observation period, animals were observed during the infusion and the findings were recorded. The day of the first dosing was designated as day 1.

2) Body weight

The body weights were measured at arrival, grouping and once a week during the experimental period. On day 29, the body weights were measured after an overnight fasting.

3) Food intake

The food intake was measured once a week. Weighed food was given to each cage, and the remaining quantity on next day was subtracted to calculate the mean daily consumption (g/head/day).

4) Ion level

In the ion levels were measured at 10 a.m. daily. The ion meter (Air ion counter, Alpha Lab Inc., USA) was measured by provided in the sponsor

6. Clinical pathology**1) Urine collection and blood sampling****(1) Urine analysis**

The urinalysis was measured at once a week using a urine measuring stick.

(2) Blood sampling

Animals were fasted for 16 hours (with water available) prior to sample collection. On the day of scheduled necropsy, blood samples were collected from the posterior vena cava of all animals under deep ether anesthesia.

Tests	Blood sample	Collecting vessel
Hematology	~ 0.3 mL	EDTA-3K CBC bottle
Serum biochemistry	≥ 0.5 mL	Vacutainer tube with clot activator

2) Hematological test

Red blood cell (RBC)	Platelet count (PLT)
Haematocrit (HCT)	Reticulocytes (RET)
Haemoglobin concentration (HGB)	White blood cell (WBC)
Mean corpuscular volume (MCV)	Neutrophil (NEU)
Mean cell hemoglobin (MCH)	Lymphocyte (LYM)
Mean cell hamoglobin concentration (MCHC)	Monocyte (MONO)
Red cell distribution width (RDW)	Eosinophil (EOS)
Hb conc. distribution width (HDW)	Basophil (BASO)
Mean platelet volume (MPV)	Large unstained cells (LUC)

3) Parameters of serum biochemistry test

Aspartate aminotransferase (AST)	Albumin (ALB)
Alanine aminotransferase (ALT)	Albumin/Globulin ratio (A/G ratio)
Alkaline phosphatase (ALP)	Blood urea nitrogen (BUN)

Creatine phosphokinase (CPK)	Creatinine (CRE)
Total bilirubin (TBIL)	Inorganic phosphorus (IP)
Glucose (GLU)	Calcium ion (Ca ²⁺)
Total cholesterol (TCHO)	Sodium ion (Na ⁺)
Triglyceride (TG)	Potassium (K ⁺)
Total protein (TP)	Chloride ion (Cl ⁻)

7. Histopathology

1) Necropsy

After blood sampling, the animals were sacrificed by exsanguination from the vena cava and aorta. Nasal, trachea, lungs, liver, kidneys, spleen, prostate, testis (ovary), uterus and eyes were removed, weighed and preserved. All animals were preserved in 10 % neutral buffered formalin, except eyes in Davidson's fixative, and testes and epididymides in Bouin's fixative.

2) Histopathologic examination

Slides of all fixed organs and tissues collected at scheduled necropsy from all animals were examined by the external measure agency (Kangwon national University, veterinary). All animals were performed H&E staining and histopathological examination.

8. Statistical analysis

Data was assumed to be normally distributed and analyzed by parametric One-Way ANOVA. When the result of ANOVA is significant, and when more than 50 % of data sets were met the assumption of homogeneity of variance, then the data were analyzed by *Duncan test* as a post hoc test. When more than 50 % of data sets were not met the assumption of homogeneity of variance, then the data were analyzed by non parametric statistics or analyzed by Dunnett T3 test as a post hoc test to find out which group is significantly different from control group.

For the histopathological examination data, the rank transformation was performed and analyzed by the non-parametric Kruskal-Wallis' H-test. When there are statistically significant differences between groups, then the *Mann-Whitney U-test* was used to find out which group is significantly different from control group.

Data were statistically analyzed with the commercial program SPSS 10.1K, and the significance level was set at $P < 0.05$.

Results

Animal death

No signs were observed by test article treatment.

Clinical sign

No signs were observed by test article treatment.

Body weights (Figure 1; Table 1; Appendix 1)

Food consumptions of male at 60 and 120 mg/kg/day were lower or statistically significantly lower than that of control. In females, food consumptions at 120 mg/kg/day on day 13 were statistically significantly lower than that of control. This explains the low body weight and weight gain.

After the 2-week recovery, there were no significant differences between the treatment groups and control group.

Food intake (Figure 2; Table 2; Appendix 2)

Results of food intake, the ion generating module HADES inhalation group was not different from vehicle control group.

Ion level (Table 3; Appendix 3)

Results of ion level, the ion generating module HADES inhalation group was not different from vehicle control group. During the experimental period, the ion generating module HADES inhalation group was determined that the cation average level was 1542 and the anion average level was -1537.

Urinalysis (Appendix 4)

Results of urinalysis, the ion generating module HADES inhalation group was not different from vehicle control group.

Organ weight (Figure 3; Table 4; Appendix 5)

Results of organ weight, the ion generating module HADES inhalation group was not significantly different from vehicle control group compared with all measurement organ (testis, prostate, ovary, uterus, kidneys, spleen, lungs and liver).

Hematology test (Table 5; Appendix 6)

Results of hematology test, the ion generating module HADES inhalation group was not significantly different from vehicle control group compared with all measurement items.

Serum biochemistry test (Table 6; Appendix 7)

Results of AST, the ion generating module HADES inhalation group were statistically significantly decreased to compared with vehicle control group in both sex animals ($P<0.05$).

Results of CPK, the ion generating module HADES inhalation group were statistically significantly decreased to compared with vehicle control group in female rats($P<0.05$). But, male rats were not significantly different from vehicle control group.

Results of TG, the ion generating module HADES inhalation group were statistically significantly increased to compared with vehicle control group in male rats($P<0.05$). But, female rats were not significantly different from vehicle control group.

Results of Ca, the ion generating module HADES inhalation group were statistically significantly increased to compared with vehicle control group in male rats($P<0.05$). But, female rats were not significantly different from vehicle control group.

Results of Cl, the ion generating module HADES inhalation group were statistically significantly decreased to compared with vehicle control group in female rats($P<0.05$). But, male rats were not significantly different from vehicle control group.

Results of other item, the ion generating module HADES inhalation group was not significantly different from vehicle control group.

Histopathological examination (Table 7; Appendix 8)

Results of male histopathological examination, the vehicle control group was observed in alveolitis by hemoglobin crystal because of lungs observed in 1 rye local alveolitis. The kidneys were observed in 1 rye local nephropathy, 2 rye focal basophilic tubules bunch and 1 rye cortex localized mineral deposits. The prostate was observed 2 rye interstitial lymphocyte infiltrations in minor levels. There was observed no abnormal findings in the vehicle control group in other organs.

The ion generating module HADES inhalation group was observed in 1 rye minor bronchial lamina propria and lymphoid infiltration of mucosal tissue. But the lungs were observed no abnormal findings. The prostate was observed in 1 rye minor interstitial lymphocyte infiltration. There was observed no abnormal findings in other organs.

Results of female histopathological examination, the vehicle control group was observed in 1 rye minor bronchial lamina propria and lymphocyte infiltration in tissue. The lungs observed in 1 rye local alveolitis and 1 rye lymphocyte infiltration around the blood vessels. The liver observed in 1 rye local multiple monocyte infiltration. The uterus was observed in 4 rye hydrometra in one or both sites. There was observed no abnormal findings in other organs.

The ion generating module HADES inhalation group was observed in focal area of tumor cell metastasis in liver. The kidneys were observed in 1 rye minor local mineral infiltration. The spleen was observed in 1 rye tumor tissue which accounts for more than 70 % of the spleen pseudocyst. The uterus was observed in 3 rye hydrometra. There was observed no abnormal findings in other organs.

Discussion and Conclusion

This study was performed to evaluate the inhalation toxicity by ion generating module when when exposed by ion generating module HADES for 4 weeks in Sprague-Dawley rats.

Observation and examination items were as follows, and the results of the treatment groups were compared with those of the vehicle control group: clinical signs, animal death, body weight changes, food intake, urinalysis, organ weight, hematology, clinical biochemistry and histopathologic examination.

The results are summarized as follows.

The death animal, clinical sign, food intake, urinalysis, organ weight and hematology test were not significantly different from the ion generating module HADES inhalation group and vehicle control group.

Results of ion level, vehicle control group were not exposed in ion. But ion generating module HADES inhalation group were exposed in ion. Therefore, we were considered to be composed of the ion generation according to ion generating module.

Results of serum biochemistry test, the ion generating module HADES inhalation group were statistically significantly decreased to both sex animals ($P<0.05$) in AST. Also, it was statistically significantly decreased ($P<0.05$) to female rat in CPK and Cl⁻. And it was statistically significantly increased ($P<0.05$) to male rat in TG and Ca²⁺. However, when on the basis of reference¹⁾, and all changes within the normal range, because it was determined that the change was due to the test article has no such change.

Results of histopathological examination, both sex animals were observed in all organs examined abnormalities associated with the inhalation of the HADES. Only, the vehicle control group was observed in both sex animals that the lung observed in local alveolitis or lymphocyte infiltration around the blood vessels. The local nephropathy, focal basophilic thrombi bunch and localized mineral deposit were often observed in the rats of normal spontaneous and the test article was independent. And they were mainly observed in male in the vehicle control group.

Accounts for 70 % of the spleen cortex was observed in the splenic tumor, the cell nuclei of chromatin heterochromatic, and shape of the round or oval or somewhat irregular, and is relatively brightly observed. It is unknown boundary between cells is basophilic cytoplasm. The shape of this tumor was determined by mononuclear leukemia. The mononuclear leukemia was known to be spontaneous incidence of tumor in rat's spleen associated mononuclear-macrophage system.

The local abnormal cells observed in liver such as the cancer cell in spleen. They were determined to have been transferred from the spleen to the liver.

The hydrometra was observed to a similar degree and frequency in both vehicle control group and ion generating module HADES inhalation group in uterus. Often associated with the hydrometra of property cycle and the uterine gland secretion was appeared disastrous cycle.

When inhaled as the HADES, the examined all organs (nosal, trachea, lungs, liver, kidneys, spleen, ulterus, ovary, prostate, testis and eyes) were determined to not cause any toxicity.

Based on the results, the test article ion generating module HADES was not different from vehicle control group in all mesurement items when administered daily by inhalation to Sprague-Dawley rats for 8 days. Therefore, the ion generating module HADES was determined that there was no difference for toxicity.

REFERENCES

1. Zhong-Ze Han, Hong-De Xu, Kwang-Ho Kim, Tae-Hwan Ahn, Jin-Sook Bae, Ji-Young Lee, Ki-Hyun Gil, Joo-Young Lee, Su-Jung Woo, Hyun-Jung Yoo, Hyun-Kul Lee, Kap-Ho Kim, Chan-Koo Park, Hu-Song Zhang and Si-Whan Song (2010): Reference data of the main physiological parameters in control Sprague-Dawley rats from pre-clinical toxicity studies, *Lab. Anim. Res.*, 26(2): 153-164
2. Hamlin and Banas (1990). Spleen, Lymph Nodes and Thymus. In: 'Pathology of the Fischer Rat'. Boorman GA, Eustis SL, Elwell MR, Montgomery, Jr. CA, MacKenzie WF ed., Academic press, Inc. London, pp369-393

UNITS AND ABBREVIATIONS

Note: The following lists of codes, abbreviations and units are used by Chemon Inc.
Some, but not necessarily all, of this information may be needed for this report.

%	Percent	hr	Hour
°	Degree	min	Minute
C	Celsius	sec	Second
L	Liter	rpm	Revolution per Minute
dL	Deciliter	RCF	Relative Centrifugal Force
mL	Milliliter	SD	Standard Deviation
µL	Microliter	CV	Coefficient of Variation
g	Gram	RE	Relative Error
kg	Kilogram	RH	Relative Humidity
mg	Milligram	M	Male
µg	Microgram	F	Female
ng	Nanogram	NA	Not Applicable
m	Meter	N	Number
cm	Centimeter	SPF	Specific Pathogen Free
mm	Millimeter	TK	Toxicokinetic
µm	Micrometer	PK	Pharmacokinetic
ppm	Parts per million	AUC	Area Under the Curve
ppb	Parts per billion	C_{max}	Maximum Concentration
wk	Week	T_{max}	Time at Maximum Concentration
d	Day	t_{1/2}	Half-life
GLP	Good Laboratory Practice Regulation	SOP	Standard Operating Procedures
QAU	Quality Assurance Unit	ICH	International Conference on Harmonization
OECD	Organization for Economic Co-operation and Development	KFDA	Korea Food and Drug Administration
IACUC	Institutional Animal Care and Use Committee	SPSS	Statistical Package for the Social Sciences
HPLC	High-Performance Liquid Chromatography	LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry

UNITS AND ABBREVIATIONS

Note: The following lists of codes, abbreviations and units are used by Chemon Inc.
Some, but not necessarily all, of this information may be needed for this report.

A/G	Albumin/Globulin ratio	Li	Lithium
ALB	Albumin	LUC	Large unstained cell
ALP	Alkaline phosphatase	LYM	Lymphocytes
ALT	Alanine aminotransferase	MCH	Mean corpuscular hemoglobin
APTT	Activated partial thromboplastin time	MCHC	Mean corpuscular hemoglobin concentration
AST	Aspartate aminotransferase	MCV	Mean corpuscular volume
BASO	Basophils	MONO	Monocytes
BIL	Bilirubin	MPV	Mean platelet volume
BUN	Blood urea nitrogen	Na⁺	Sodium
Ca²⁺	Calcium	NEU	Neutrophils
Cl⁻	Chloride	NIT	Nitrite
CPK	Creatine phosphokinase	OB	Occult blood
CRE	Creatinine	pH	Potential of hydrogen
EOS	Eosinophils	PLT	platelet count
Fe²⁺	Iron	PRO	Protein
GGT	Gamma glutamyl transpeptidase	PT	Prothrombin time
GLU	Glucose	RBC	Red blood cell
HCT	Hematocrit	RDW	Red cell distribution width
HDL	High density lipoprotein cholesterol	RET	Reticulocytes
HDW	Hemoglobin distribution width	SG	Specific gravity
HGB	Hemoglobin	TBIL	Total bilirubin
IP	Inorganic phosphorus	TTCHO	Total cholesterol
K⁺	Potassium	TG	Triglyceride
KET	Ketone body	TP	Total protein
LDL	Low density lipoprotein cholesterol	URO	Urobilinogen
LDH	Lactate dehydrogenase	WBC	White blood cell

FIGURES

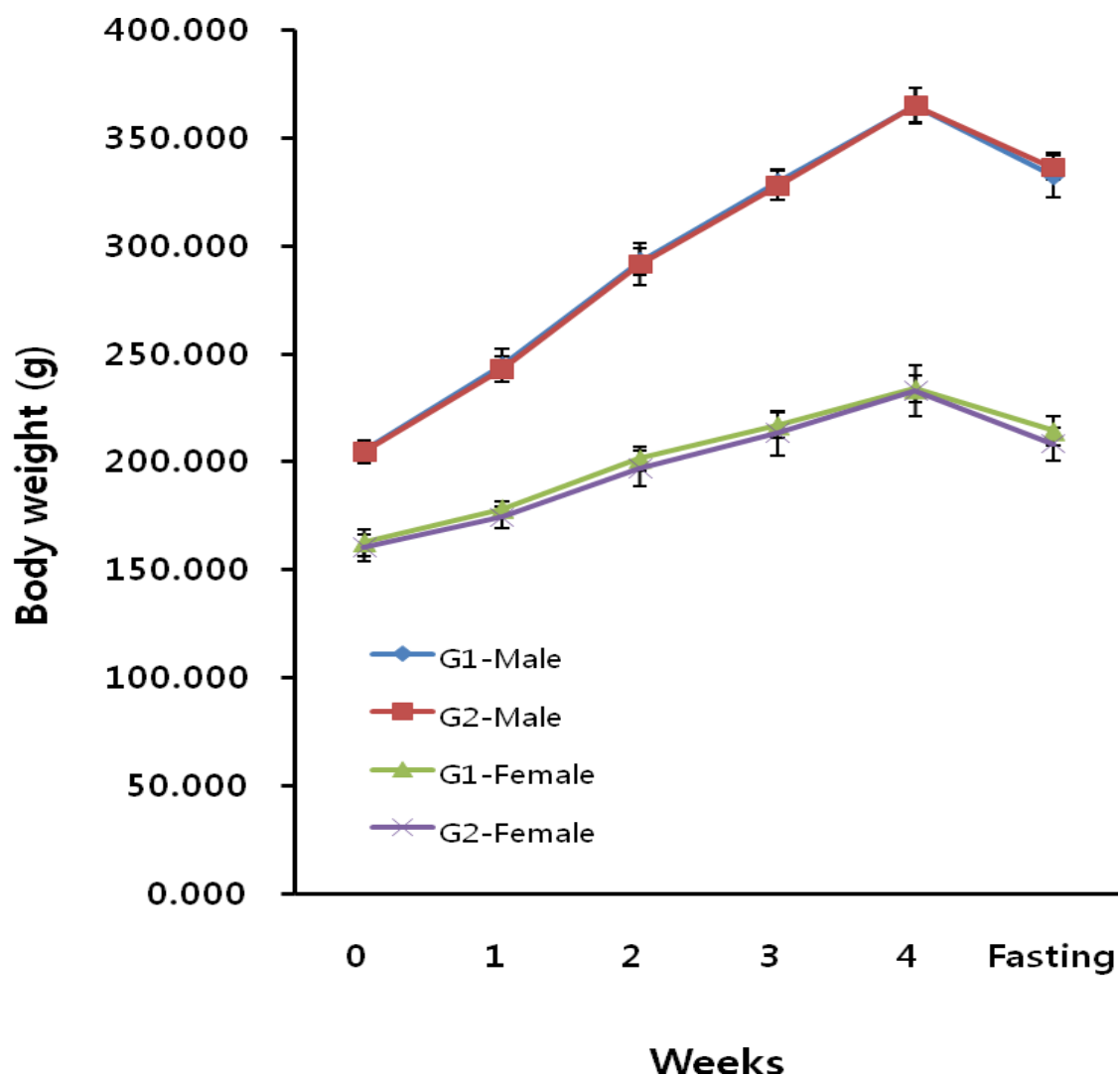


Figure 1. Changes of body weight in SD rats.

Data are expressed as Mean \pm S.D. The results were statistically analyzed by *ONE-WAY ANOVA*.

G1: Vehicle control (n=6/6)

G2: Test article (Ionized air blower HADES, n=6/6)

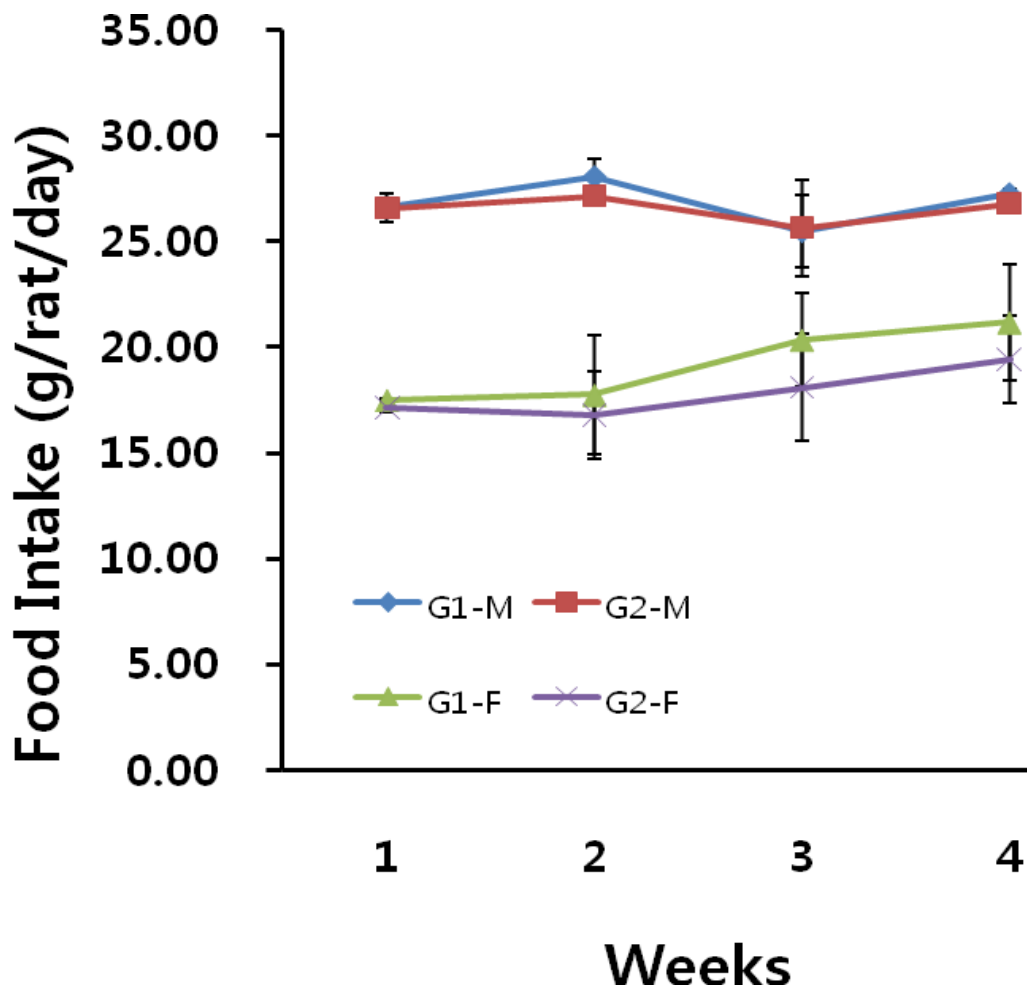


Figure 2. Effects of the test article on food intake in SD rats.

Data are expressed as MEAN±S.D. The results were statistically analyzed by *ONE-WAY ANOVA* methods.

G1: Vehicle control (n=6/6)

G2: Test article (Ionized air blower HADES, n=6/6)

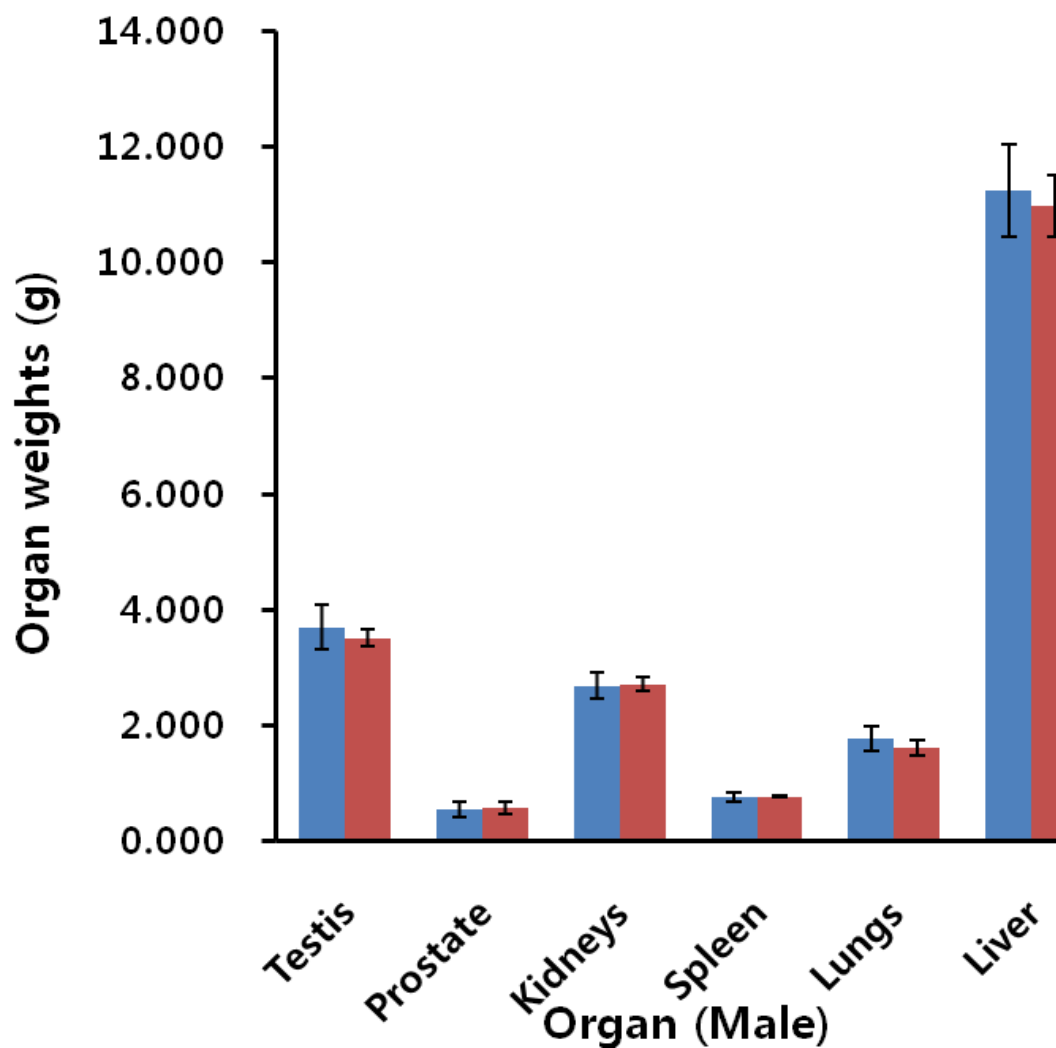


Figure 3. Effects of the test article on organ weights in SD rats (male).

Data are expressed as MEAN±S.D. The results were statistically analyzed by *ONE-WAY ANOVA* methods.

G1: Vehicle control (n=6/6)

G2: Test article (Ionized air blower HADES, n=6/6)

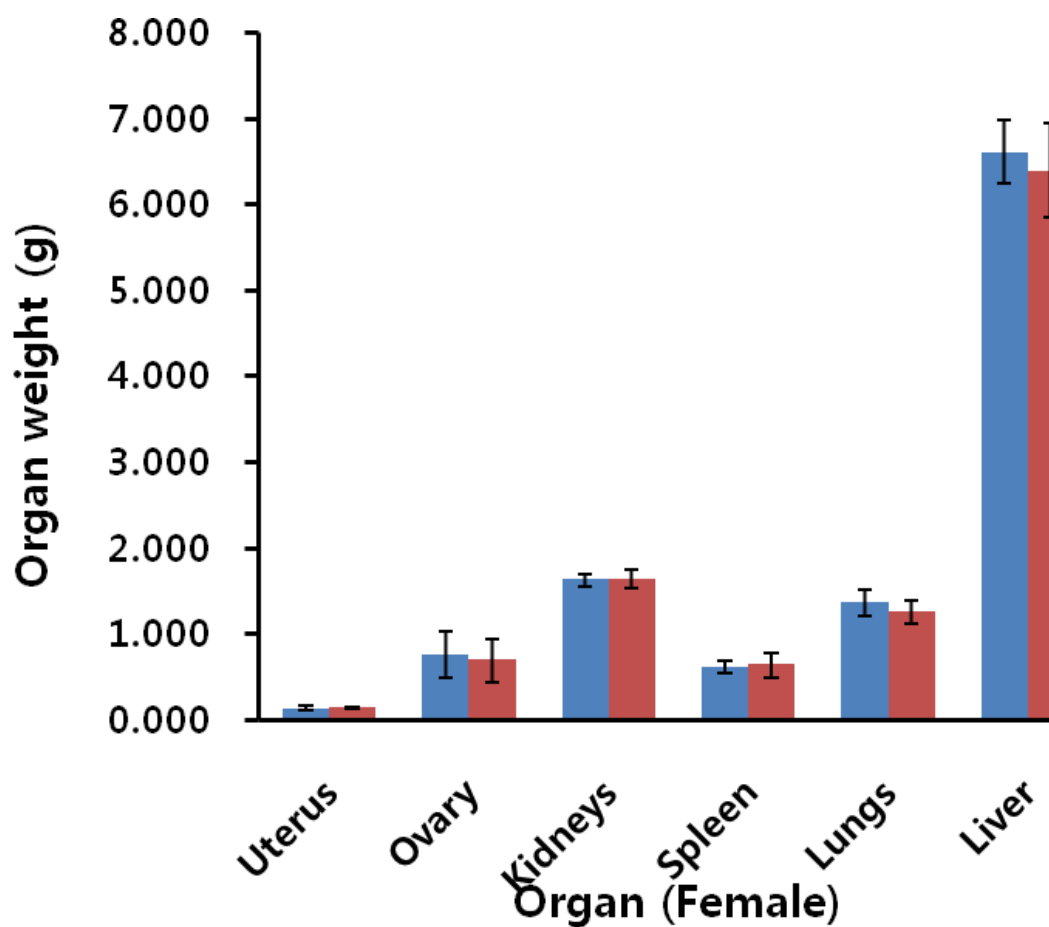


Figure 4. Effects of the test article on organ weights in SD rats (female).

Data are expressed as MEAN±S.D. The results were statistically analyzed by *ONE-WAY ANOVA* methods.

G1: Vehicle control (n=6/6)

G2: Test article (Ionized air blower HADES, n=6/6)

TABLES

Table 1. Body weights

BODY WEIGHTS (g)			MALE
DAYS	GROUPS		
	G1 (0)	G2 (HADES)	
1	205.37±4.56	204.58±5.16	
7	244.64±7.69	243.15±6.02	
14	292.94±6.24	291.62±9.70	
20	329.60±5.90	327.99±6.83	
28	365.22±8.13	365.29±8.06	
30	332.74±10.32	336.44±5.59	
GAINS	159.85±1.44	160.71±1.78	
N	6	6	

BODY WEIGHTS (g)			FEMALE
DAYS	GROUPS		
	G1 (0)	G2 (HADES)	
1	162.69±6.21	160.43±6.13	
7	178.27±3.71	174.37±5.23	
14	201.45±5.68	197.15±8.39	
20	216.99±5.98	213.42±10.48	
28	233.96±6.06	233.05±11.74	
30	214.32±6.74	208.45±7.73	
GAINS	71.28±1.04	72.62±2.78	
N	6	6	

The day of first treatment was designated day 1.
Gain is body weight on day 28 - body weight on day.
Data are expressed as Mean ± S.D.

Table 2. Food intake

FOOD INTAKE (g/rat/day)			MALE
DAYS	GROUPS		
	G1 (0)	G2 (HADES)	
7	26.59±0.67	26.56±0.12	
14	28.05±0.87	27.12±0.43	
20	25.48±1.73	25.64±2.28	
28	27.25±0.23	26.78±0.08	
N	6	6	

FOOD INTAKE (g/rat/day)			FEMALE
DAYS	GROUPS		
	G1 (0)	G2 (HADES)	
7	17.48±0.07	17.11±0.23	
14	17.73±2.80	16.75±2.08	
20	20.34±2.20	18.08±2.54	
28	21.17±2.74	19.43±2.07	
N	6	6	

The day of first treatment was designated day 1.
Data are expressed as Mean ± S.D.

Table 3. Ion levels

DAYS	ION LEVELS (CATHION)		MALE
	GROUPS		
	G1 (0)	G2 (HADES)	
1	0.00±0.00	1999.00±0.00	
2	0.00±0.00	1999.00±0.00	
3	0.00±0.00	1999.00±0.00	
4	0.00±0.00	1659.00±480.83	
5	0.00±0.00	199.00±0.00	
6	0.00±0.00	1999.00±0.00	
7	0.00±0.00	976.00±98.99	
8	0.00±0.00	1178.00±349.31	
9	0.00±0.00	1000.00±15.56	
10	0.00±0.00	1171.00±209.30	
11	0.00±0.00	1014.50±150.61	
12	0.00±0.00	1127.50±103.94	
13	0.00±0.00	1355.50±219.91	
14	0.00±0.00	1999.00±0.00	
15	0.00±0.00	1999.00±0.00	
16	0.00±0.00	1999.00±0.00	
17	0.00±0.00	1999.00±0.00	
18	0.00±0.00	1999.00±0.00	
19	0.00±0.00	1279.50±171.83	
20	0.00±0.00	1133.00±237.59	
21	0.00±0.00	1207.00±8.49	
22	0.00±0.00	1068.50±212.84	
23	0.00±0.00	1194.00±9.90	
24	0.00±0.00	1264.50±51.62	
25	0.00±0.00	1999.00±0.00	
26	0.00±0.00	1999.00±0.00	
27	0.00±0.00	1999.00±0.00	
28	0.00±0.00	1999.00±0.00	
N	6	6	

Data are expressed as Mean ± S.D.

<CONTINUED>

Table 3. Ion levels

DAYS	ION LEVELS (ANION)		MALE
	GROUPS		
	G1 (0)	G2 (HADES)	
1	0.00±0.00	-1999.00±0.00	
2	0.00±0.00	-1999.00±0.00	
3	0.00±0.00	-1999.00±0.00	
4	0.00±0.00	-1999.00±0.00	
5	0.00±0.00	-1999.00±0.00	
6	0.00±0.00	-1999.00±0.00	
7	0.00±0.00	-952.00±83.44	
8	0.00±0.00	-1068.50±330.22	
9	0.00±0.00	-908.00±91.92	
10	0.00±0.00	-1111.50±154.86	
11	0.00±0.00	-997.00±22.63	
12	0.00±0.00	-1096.50±161.93	
13	0.00±0.00	-1290.00±55.15	
14	0.00±0.00	-1999.00±0.00	
15	0.00±0.00	-1999.00±0.00	
16	0.00±0.00	-1999.00±0.00	
17	0.00±0.00	-1999.00±0.00	
18	0.00±0.00	-1999.00±0.00	
19	0.00±0.00	-1140.50±217.08	
20	0.00±0.00	-1060.00±173.95	
21	0.00±0.00	-1139.50±185.97	
22	0.00±0.00	-994.00±147.08	
23	0.00±0.00	-997.00±8.49	
24	0.00±0.00	-1170.00±199.40	
25	0.00±0.00	-1999.00±0.00	
26	0.00±0.00	-1999.00±0.00	
27	0.00±0.00	-1999.00±0.00	
28	0.00±0.00	-1999.00±0.00	
N	6	6	

Data are expressed as Mean ± S.D.

<CONTINUED>

Table 3. Ion levels

DAYS	ION LEVELS (CATHION)		FEMALE
	GROUPS		
	G1 (0)	G2 (HADES)	
1	0.00±0.00	1281.50±601.75	
2	0.00±0.00	1066.00±26.87	
3	0.00±0.00	1100.00±468.10	
4	0.00±0.00	1110.50±252.44	
5	0.00±0.00	1276.00±346.48	
6	0.00±0.00	1071.00±339.41	
7	0.00±0.00	1999.00±0.00	
8	0.00±0.00	1999.00±0.00	
9	0.00±0.00	1999.00±0.00	
10	0.00±0.00	1999.00±0.00	
11	0.00±0.00	1999.00±0.00	
12	0.00±0.00	1999.00±0.00	
13	0.00±0.00	1999.00±0.00	
14	0.00±0.00	1999.00±0.00	
15	0.00±0.00	1256.00±63.64	
16	0.00±0.00	935.00±156.98	
17	0.00±0.00	1199.50±143.54	
18	0.00±0.00	1163.50±78.49	
19	0.00±0.00	1999.00±0.00	
20	0.00±0.00	1999.00±0.00	
21	0.00±0.00	1999.00±0.00	
22	0.00±0.00	1999.00±0.00	
23	0.00±0.00	1999.00±0.00	
24	0.00±0.00	1999.00±0.00	
25	0.00±0.00	1106.50±133.64	
26	0.00±0.00	1142.00±83.44	
27	0.00±0.00	901.00±2.83	
28	0.00±0.00	1052.50±78.49	
N	6	6	

Data are expressed as Mean ± S.D.

<CONTINUED>

Table 3. Ion levels

DAYS	ION LEVELS (ANION)		FEMALE
	GROUPS		
	G1 (0)	G2 (HADES)	
1	0.00±0.00	-1235.50±516.90	
2	0.00±0.00	-1180.00±186.68	
3	0.00±0.00	-1124.50±400.93	
4	0.00±0.00	-997.50±149.20	
5	0.00±0.00	-1236.50±358.50	
6	0.00±0.00	-1035.50±234.05	
7	0.00±0.00	-1999.00±0.00	
8	0.00±0.00	-1999.00±0.00	
9	0.00±0.00	-1999.00±0.00	
10	0.00±0.00	-1999.00±0.00	
11	0.00±0.00	-1999.00±0.00	
12	0.00±0.00	-1999.00±0.00	
13	0.00±0.00	-1999.00±0.00	
14	0.00±0.00	-1035.50±193.04	
15	0.00±0.00	-1195.50±17.68	
16	0.00±0.00	-1042.50±7.78	
17	0.00±0.00	-1021.00±176.78	
18	0.00±0.00	-1034.00±94.75	
19	0.00±0.00	-1999.00±0.00	
20	0.00±0.00	-1999.00±0.00	
21	0.00±0.00	-1999.00±0.00	
22	0.00±0.00	-1999.00±0.00	
23	0.00±0.00	-1999.00±0.00	
24	0.00±0.00	-1999.00±0.00	
25	0.00±0.00	-1074.00±60.81	
26	0.00±0.00	-1091.50±147.79	
27	0.00±0.00	-885.00±16.97	
28	0.00±0.00	-1021.00±14.14	
N	6	6	

Data are expressed as Mean ± S.D.

<END>

Table 4. Organ weights

ORGAN WEIGHTS (g)			MALE
ORGAN	GROUPS		
	G1 (0)	G2 (HADES)	
Testis	3.697±0.379	3.520±0.155	
Prostate gland	0.548±0.145	0.574±0.111	
Kidney	2.692±0.223	2.719±0.120	
Spleen	0.765±0.071	0.766±0.015	
Lung	1.771±0.205	1.614±0.134	
Liver	11.249±0.811	10.980±0.525	
N	6	6	
ORGAN WEIGHTS (g)			FEMALE
ORGAN	GROUPS		
	G1 (0)	G2 (HADES)	
Ovary	0.135±0.027	0.144±0.013	
Uterus	0.762±0.275	0.698±0.253	
Kidney	1.631±0.070	1.639±0.107	
Spleen	0.615±0.067	0.644±0.144	
Lung	1.365±0.152	1.255±0.142	
Liver	6.618±0.371	6.405±0.545	
N	6	6	

Data are expressed as Mean ± S.D.

Table 5. Hematological test

		HEMATOLOGICAL TEST		MALE
TESTS	UNITS	GROUPS		
		G1 (0)	G2 (HADES)	
WBCB	10 ³ /μL	7.9±1.2	7.4±1.1	
RBC	10 ⁶ /μL	8.6±0.3	8.4±0.3	
HGB	g/dL	15.5±0.4	15.4±0.3	
HCT	%	47.9±1.2	47.6±0.7	
MCV	fL	56.0±1.4	56.6±1.9	
MCH	Pg	18.1±0.5	18.4±0.7	
MCHC	g/dL	32.2±0.2	32.4±0.3	
RDW	%	11.7±0.4	11.6±0.3	
HDW	g/dL	2.5±0.1	2.4±0.1	
PLT	10 ³ /μL	1175.5±89.6	1187.5±71.6	
MPV	fL	6.6±0.2	6.6±0.2	
NEU	%	12.7±6.4	14.3±2.9	
LYM	%	82.7±6.4	81.9±2.8	
MONO	%	2.4±0.8	2.3±0.4	
EOS	%	1.0±1.4	0.5±0.2	
BASO	%	0.2±0.1	0.2±0.1	
LUC	%	1.0±0.9	0.9±0.2	
NEU	10 ³ /μL	1.0±0.5	1.1±0.3	
LYM	10 ³ /μL	6.5±1.3	6.1±0.8	
MONO	10 ³ /μL	0.2±0.0	0.2±0.0	
EOS	10 ³ /μL	0.1±0.1	0.0±0.0	
LUC	10 ³ /μL	0.1±0.1	0.1±0.0	
BASO	10 ³ /μL	0.0±0.0	0.0±0.0	
RET	%	3.1±0.3	2.9±0.3	
N		6	6	

Data are expressed as Mean ± S.D.

<CONTINUED>

Table 5. Hematological test

		HEMATOLOGICAL TEST		FEMALE
TESTS	UNITS	GROUPS		
		G1 (0)	G2 (HADES)	
WBCB	10 ³ /μL	3.6±0.5	3.7±1.0	
RBC	10 ⁶ /μL	8.2±0.3	8.2±0.2	
HGB	g/dL	14.8±0.4	14.7±0.2	
HCT	%	44.6±0.8	44.5±0.7	
MCV	fL	54.4±1.0	54.5±1.6	
MCH	Pg	18.0±0.3	18.1±0.5	
MCHC	g/dL	33.2±0.5	33.1±0.2	
RDW	%	10.9±0.3	11.3±0.4	
HDW	g/dL	2.3±0.1	2.4±0.2	
PLT	10 ³ /μL	1099.0±170.8	1025.7±247.3	
MPV	fL	6.8±0.4	7.1±0.4	
NEU	%	16.7±7.1	14.0±4.9	
LYM	%	79.4±7.1	81.9±5.7	
MONO	%	2.4±0.4	2.6±0.9	
EOS	%	0.8±0.3	0.9±0.4	
BASO	%	0.1±0.1	0.2±0.1	
LUC	%	0.6±0.2	0.7±0.1	
NEU	10 ³ /μL	0.6±0.3	0.5±0.2	
LYM	10 ³ /μL	2.8±0.4	3.0±0.9	
MONO	10 ³ /μL	0.1±0.0	0.1±0.0	
EOS	10 ³ /μL	0.0±0.0	0.0±0.0	
LUC	10 ³ /μL	0.0±0.0	0.0±0.0	
BASO	10 ³ /μL	0.0±0.0	0.0±0.0	
RET	%	3.0±0.5	2.9±0.3	
N		6	6	

Data are expressed as Mean ± S.D.

<END>

Table 6. Clinical biochemistry test

		CLINICAL BIOCHEMISTRY TEST		MALE
TESTS	UNITS	GROUPS		
		G1 (0)	G2 (HADES)	
AST	U/L	147.1±11.0	129.9±14.8*	
ALT	U/L	28.7±2.7	29.5±2.8	
ALP	U/L	154.2±19.0	156.1±39.1	
CPK	U/L	786.8±131.2	689.7±132.0	
TBIL	mg/dL	0.1±0.0	0.1±0.0	
GLU	mg/dL	119.7±16.5	114.2±7.0	
TCHO	mg/dL	78.7±9.6	74.7±9.2	
TG	mg/dL	41.3±5.5	50.8±8.1*	
TP	g/dL	5.9±0.1	6.0±0.2	
ALB	g/dL	3.1±0.1	3.2±0.1	
A/G ratio		1.1±0.1	1.1±0.0	
BUN	mg/dL	13.6±0.6	13.9±0.8	
CRE	mg/dL	0.4±0.0	0.4±0.0	
IP	mg/dL	8.9±0.2	8.8±0.4	
Ca ²⁺	mg/dL	9.3±0.1	9.5±0.1*	
Na ⁺	mmol/L	143.0±1.1	143.9±0.5	
K ⁺	mmol/L	4.5±0.1	4.5±0.2	
Cl ⁻	mmol/L	99.6±1.0	100.1±0.9	
N		6	6	

Data are expressed as Mean ± S.D.

* Significant difference at $P < 0.05$ levels compared with the normal control.

<CONTINUED>

Table 6. Clinical biochemistry test

		CLINICAL BIOCHEMISTRY TEST		FEMALE
TESTS	UNITS	GROUPS		
		G1 (0)	G2 (HADES)	
AST	U/L	118.2±10.0	103.8±5.9*	
ALT	U/L	25.1±2.5	24.4±2.5	
ALP	U/L	95.6±15.0	107.7±15.7	
CPK	U/L	437.8±107.1	237.0±69.5*	
TBIL	mg/dL	0.1±0.0	0.1±0.0	
GLU	mg/dL	95.3±7.1	99.7±5.7	
TCHO	mg/dL	87.5±23.0	71.2±9.5	
TG	mg/dL	33.8±5.8	31.7±2.7	
TP	g/dL	5.7±0.2	5.8±0.2	
ALB	g/dL	3.1±0.1	3.2±0.1	
A/G ratio		1.2±0.1	1.3±0.1	
BUN	mg/dL	16.7±1.3	17.6±1.4	
CRE	mg/dL	0.4±0.0	0.5±0.0	
IP	mg/dL	7.1±0.4	7.0±0.9	
Ca ²⁺	mg/dL	9.2±0.1	9.3±0.2	
Na ⁺	mmol/L	142.6±0.7	142.8±1.0	
K ⁺	mmol/L	4.1±0.2	4.3±0.5	
Cl ⁻	mmol/L	102.5±0.7	103.9±1.1*	
N		6	6	

Data are expressed as Mean ± S.D.

* Significant difference at $P < 0.05$ levels compared with the normal control.

<END>

Table 7. Summary of the histopathological lesions

HISTOPATHOLOGICAL LESIONS		MALE	
ORGAN		GROUPS	
		G1 (0)	G2 (HADES)
Nasal cavity	No specific lesion	6/6	6/6
Trachea	No specific lesion	6/6	6/5
	Cell infiltration, lymphocytic, LP&submucosa	0/6	1/6
Lung	No specific lesion	5/6	6/6
	Inflammatory foci, chronic	1/6	0/6
	Cell infiltration, lymphoid cells, perivascular	0/6	0/6
	Hemoglobin pneumonia, focal	0/6	0/6
Liver	No specific lesion	6/6	6/6
	Cell infiltration, mononuclear cell, (multi)focal	0/6	0/6
	Metastatic tumor cells, focal	0/6	0/6
Kidney	No specific lesion	3/6	6/6
	Focal nephropathy, (multi)focal	1/6	0/6
	Basophilic tubules, (multi)focal	2/6	0/6
	Mineralization, (multi)focal	0/6	0/6
Spleen	No specific lesion	6/6	6/6
	Mononuclear cell leukemia	0/6	0/6
Testis	No specific lesion	6/6	6/6
Epididymis	No specific lesion	6/6	6/6
Prostate gland	No specific lesion	4/6	5/6
	Lymphoid cell infiltration, interstitium	2/6	1/6
Eyes	No specific lesion	6/6	6/6
N		6	6

<CONTINUED>

Table 7. Summary of the histopathological lesions

HISTOPATHOLOGICAL LESIONS		FEMALE	
ORGAN		GROUPS	
		G1 (0)	G2 (HADES)
Nasal cavity	No specific lesion	6/6	6/6
Trachea	No specific lesion	5/6	6/6
	Cell infiltration, lymphocytic, LP&submucosa	1/6	0/6
Lung	No specific lesion	4/6	6/6
	Inflammatory foci, chronic	1/6	0/6
	Cell infiltration, lymphoid cells, perivascular	1/6	0/6
	Hemoglobin pneumonia, focal	0/6	0/6
Liver	No specific lesion	5/6	5/6
	Cell infiltration, mononuclear cell, (multi)focal	1/6	0/6
	Metastatic tumor cells, focal	0/6	1/6
Kidney	No specific lesion	6/6	5/6
	Focal nephropathy, (multi)focal	0/6	0/6
	Basophilic tubules, (multi)focal	0/6	0/6
	Mineralization, (multi)focal	0/6	1/6
Spleen	No specific lesion	6/6	5/6
	Mononuclear cell leukemia	0/6	1/6
Ovary	No specific lesion	6/6	6/6
Uterus	No specific lesion	2/6	3/6
	Hydrometra, uni-or bilateral	4/6	3/6
Eyes	No specific lesion	6/6	6/6
N		6	6

<END>

APPENDICES

Appendix 1. Individual body weights

BDOY WEIGHTS (g)							MALE
GROUP: G1 (Vehicle control)							
Animal ID	Day 1	Day 7	Day 14	Day 20	Day 28	Day 30	
1	198.79	239.04	286.30	324.07	353.19	316.40	
2	204.26	238.00	290.11	331.94	364.79	335.58	
3	202.38	238.80	286.80	328.32	365.88	331.31	
4	206.75	243.64	295.28	324.51	361.16	328.96	
5	208.30	253.08	297.21	328.72	368.48	336.38	
6	211.71	255.30	301.95	340.06	377.79	347.83	
MEAN	205.37	244.64	292.94	329.60	365.22	332.74	
S.D.	4.56	7.69	6.24	5.90	8.13	10.32	
N	6	6	6	6	6	6	
GROUP: G2 (Test article, HADES)							
Animal ID	Day 1	Day 7	Day 14	Day 20	Day 28	Day 30	
7	200.36	235.59	273.90	315.18	353.28	327.73	
8	199.97	238.31	287.78	334.70	375.32	344.63	
9	201.38	246.66	295.55	327.47	371.82	335.20	
10	203.74	239.68	294.38	328.26	362.00	339.36	
11	210.76	249.82	301.10	332.51	361.10	334.73	
12	211.29	248.81	297.00	329.83	368.24	336.97	
MEAN	204.58	243.15	291.62	327.99	365.29	336.44	
S.D.	5.16	6.02	9.70	6.83	8.06	5.59	
N	6	6	6	6	6	6	

<CONTINUED>

Appendix 1. Individual body weights

BDOY WEIGHTS (g)							FEMALE
GROUP: G1 (Vehicle control)							
Animal ID	Day 1	Day 7	Day 14	Day 20	Day 28	Day 30	
13	155.26	177.07	193.32	212.20	230.34	210.64	
14	162.21	178.25	199.70	214.19	228.11	208.25	
15	158.54	185.30	203.24	220.81	237.20	209.98	
16	163.18	174.22	206.38	217.79	234.39	217.63	
17	163.29	177.23	197.58	210.46	229.49	213.02	
18	173.63	177.57	208.49	226.50	244.23	226.37	
MEAN	162.69	178.27	201.45	216.99	233.96	214.32	
S.D.	6.21	3.71	5.68	5.98	6.06	6.74	
N	6	6	6	6	6	6	
GROUP: G2 (Test article, HADES)							
Animal ID	Day 1	Day 7	Day 14	Day 20	Day 28	Day 30	
19	155.60	164.79	188.17	202.49	223.96	200.71	
20	151.30	174.90	196.62	217.34	238.76	211.72	
21	160.85	172.46	189.67	198.41	214.47	196.88	
22	162.26	178.25	194.40	220.54	241.16	214.44	
23	164.11	178.69	204.48	217.19	234.15	211.42	
24	168.43	177.10	209.55	224.56	245.78	215.50	
MEAN	160.43	174.37	197.15	213.42	233.05	208.45	
S.D.	6.13	5.23	8.39	10.48	11.74	7.73	
N	6	6	6	6	6	6	

<END>

Appendix 2. Individual food intake

BDOY WEIGHTS (g)					MALE
GROUP: G1 (Vehicle control)					
Cage No.	Day 7	Day 14	Day 20	Day 28	
1	27.06	28.67	26.70	27.09	
2	26.12	27.44	24.26	27.41	
MEAN	26.59	28.05	25.48	27.25	
S.D.	0.67	0.87	1.73	0.23	
N	2	2	2	2	
GROUP: G2 (Test article, HADES)					
Cage No.	Day 7	Day 14	Day 20	Day 28	
3	26.64	27.42	24.02	26.84	
4	26.48	26.81	27.25	26.73	
MEAN	26.56	27.12	25.64	26.78	
S.D.	0.12	0.43	2.28	0.08	
N	2	2	2	2	
BDOY WEIGHTS (g)					FEMALE
GROUP: G1 (Vehicle control)					
Cage No.	Day 7	Day 14	Day 20	Day 28	
5	17.43	19.71	18.79	19.23	
6	17.53	15.75	21.90	23.10	
MEAN	17.48	17.73	20.34	21.17	
S.D.	0.07	2.80	2.20	2.74	
N	2	2	2	2	
GROUP: G2 (Test article, HADES)					
Cage No.	Day 7	Day 14	Day 20	Day 28	
7	16.94	15.28	16.28	17.96	
8	17.27	18.22	19.87	20.89	
MEAN	17.11	16.75	18.08	19.43	
S.D.	0.23	2.08	2.54	2.07	
N	2	2	2	2	

<END>

Appendix 3-1. Individual cathion levels

CATHION LEVELS								MALE
GROUP: G1								
(Vehicle control)								
Cage No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	

<CONTINUED>

Appendix 3-1. Individual cation levels

CATHION LEVELS								MALE
GROUP: G2								
(Test article, HADES)								
Cage No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
3	1999.00	1999.00	1999.00	1999.00	1999.00	1999.00	1046.00	
4	1999.00	1999.00	1999.00	1319.00	1999.00	1999.00	906.00	
MEAN	1999.00	1999.00	1999.00	1659.00	1999.00	1999.00	976.00	
S.D.	0.00	0.00	0.00	480.83	0.00	0.00	98.99	
N	2	2	2	2	2	2	2	
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
3	931.00	1011.00	1023.00	1121.00	1201.00	1511.00	1999.00	
4	1425.00	989.00	1319.00	908.00	1054.00	1200.00	1999.00	
MEAN	1178.00	1000.00	1171.00	1014.50	1127.50	1355.50	1999.00	
S.D.	349.31	15.56	209.30	150.61	103.94	219.91	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
3	1999.00	1999.00	1999.00	1999.00	1158.00	965.00	1213.00	
4	1999.00	1999.00	1999.00	1999.00	1401.00	1301.00	1201.00	
MEAN	1999.00	1999.00	1999.00	1999.00	1279.50	1133.00	1207.00	
S.D.	0.00	0.00	0.00	0.00	171.83	237.59	8.49	
N	2	2	2	2	2	2	2	
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	
3	918.00	1201.00	1301.00	1999.00	1999.00	1999.00	1999.00	
4	1219.00	1187.00	1228.00	1999.00	1999.00	1999.00	1999.00	
MEAN	1068.50	1194.00	1264.50	1999.00	1999.00	1999.00	1999.00	
S.D.	212.84	9.90	51.62	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	

<CONTINUED>

Appendix 3-1. Individual cathion levels

CATHION LEVELS							FEMALE
GROUP: G1							
(Vehicle control)							
Cage No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2

<CONTINUED>

Appendix 3-1. Individual cathion levels

CATHION LEVELS							FEMALE
GROUP: G2							
(Test article, HADES)							
Cage No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
7	856.00	1085.00	769.00	932.00	1031.00	831.00	1999.00
8	1707.00	1047.00	1431.00	1289.00	1521.00	1311.00	1999.00
MEAN	1281.50	1066.00	1100.00	1110.50	1276.00	1071.00	1999.00
S.D.	601.75	26.87	468.10	252.44	346.48	339.41	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
7	1999.00	1999.00	1999.00	1999.00	1999.00	1999.00	1201.00
8	1999.00	1999.00	1999.00	1999.00	1999.00	1999.00	981.00
MEAN	1999.00	1999.00	1999.00	1999.00	1999.00	1999.00	1091.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	155.56
N	2	2	2	2	2	2	2
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
7	1211.00	824.00	1301.00	1219.00	1999.00	1999.00	1999.00
8	1301.00	1046.00	1098.00	1108.00	1999.00	1999.00	1999.00
MEAN	1256.00	935.00	1199.50	1163.50	1999.00	1999.00	1999.00
S.D.	63.64	156.98	143.54	78.49	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
7	1999.00	1999.00	1999.00	1012.00	1201.00	903.00	1108.00
8	1999.00	1999.00	1999.00	1201.00	1083.00	899.00	997.00
MEAN	1999.00	1999.00	1999.00	1106.50	1142.00	901.00	1052.50
S.D.	0.00	0.00	0.00	133.64	83.44	2.83	78.49
N	2	2	2	2	2	2	2

<END>

Appendix 3-2. Individual anion levels

ANION LEVELS								MALE
GROUP: G1								
(Vehicle control)								
Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	

<CONTINUED>

Appendix 3-2. Individual anion levels

ANION LEVELS								MALE
GROUP: G2								
(Test article, HADES)								
Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
3	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-893.00	
4	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1011.00	
MEAN	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-952.00	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	83.44	
N	2	2	2	2	2	2	2	
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
3	-835.00	-973.00	-1002.00	-981.00	-1211.00	-1329.00	-1999.00	
4	-1302.00	-843.00	-1221.00	-1013.00	-982.00	-1251.00	-1999.00	
MEAN	-1068.50	-908.00	-1111.50	-997.00	-1096.50	-1290.00	-1999.00	
S.D.	330.22	91.92	154.86	22.63	161.93	55.15	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
3	-1999.00	-1999.00	-1999.00	-1999.00	-987.00	-937.00	-1008.00	
4	-1999.00	-1999.00	-1999.00	-1999.00	-1294.00	-1183.00	-1271.00	
MEAN	-1999.00	-1999.00	-1999.00	-1999.00	-1140.50	-1060.00	-1139.50	
S.D.	0.00	0.00	0.00	0.00	217.08	173.95	185.97	
N	2	2	2	2	2	2	2	
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	
3	-890.00	-1003.00	-1311.00	-1999.00	-1999.00	-1999.00	-1999.00	
4	-1098.00	-991.00	-1029.00	-1999.00	-1999.00	-1999.00	-1999.00	
MEAN	-994.00	-997.00	-1170.00	-1999.00	-1999.00	-1999.00	-1999.00	
S.D.	147.08	8.49	199.40	0.00	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	

<END>

Appendix 3-2. Individual anion levels

ANION LEVELS							FEMALE
GROUP: G1							
(Vehicle control)							
Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MEAN	0.00	0.00	0.00	0.00	0.00	0.00	0.00
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	2	2	2	2	2	2	2

<CONTINUED>

Appendix 3-2. Individual anion levels

ANION LEVELS								FEMALE
GROUP: G2								
(Test article, HADES)								
Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
7	-870.00	-1048.00	-841.00	-892.00	-983.00	-870.00	-1999.00	
8	-1601.00	-1312.00	-1408.00	-1103.00	-1490.00	-1201.00	-1999.00	
MEAN	-1235.50	-1180.00	-1124.50	-997.50	-1236.50	-1035.50	-1999.00	
S.D.	516.90	186.68	400.93	149.20	358.50	234.05	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	
7	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1172.00	
8	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-899.00	
MEAN	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1999.00	-1035.50	
S.D.	0.00	0.00	0.00	0.00	0.00	0.00	193.04	
N	2	2	2	2	2	2	2	
Animal ID	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
7	-1208.00	-1037.00	-1146.00	-1101.00	-1999.00	-1999.00	-1999.00	
8	-1183.00	-1048.00	-896.00	-967.00	-1999.00	-1999.00	-1999.00	
MEAN	-1195.50	-1042.50	-1021.00	-1034.00	-1999.00	-1999.00	-1999.00	
S.D.	17.68	7.78	176.78	94.75	0.00	0.00	0.00	
N	2	2	2	2	2	2	2	
Animal ID	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	
7	-1999.00	-1999.00	-1999.00	-1031.00	-1196.00	-897.00	-1031.00	
8	-1999.00	-1999.00	-1999.00	-1117.00	-987.00	-873.00	-1011.00	
MEAN	-1999.00	-1999.00	-1999.00	-1074.00	-1091.50	-885.00	-1021.00	
S.D.	0.00	0.00	0.00	60.81	147.79	16.97	14.14	
N	2	2	2	2	2	2	2	

<END>

Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 0)										MALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU	
G1 (Vehicle control)											
1	-	-	-	-	6.0	1+	≥1.030	+/-	-	-	
2	-	-	-	-	7.5	-	1.010	-	-	-	
3	-	-	-	-	7.0	-	1.015	-	-	-	
4	-	-	-	+	6.5	-	1.010	+/-	-	-	
5	-	-	-	-	5.0	-	1.010	+/-	-	-	
6	-	-	-	+	6.5	-	1.010	-	-	-	
G2 (Test article, HADES)											
7	-	-	-	-	7.0	-	1.005	-	-	-	
8	-	-	-	-	8.0	-	1.005	-	-	-	
9	-	-	-	-	6.5	-	1.005	-	-	-	
10	-	-	-	-	5.0	-	1.005	-	-	-	
11	-	-	-	+	6.5	-	1.015	+/-	-	-	
12	-	-	-	-	6.0	-	1.020	-	-	-	

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

<CONTINUED>

Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 0)									FEMALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
13	-	-	-	-	6.0	1+	≥1.030	-	-	-
14	-	-	-	-	7.0	-	1.005	-	-	-
15	-	-	-	-	5.0	-	1.0005	-	+	-
16	-	-	-	-	5.0	-	1.005	-	-	-
17	-	-	-	-	6.0	-	1.005	-	-	-
18	-	-	-	-	7.0	-	1.000	-	-	-
G2 (Test article, HADES)										
19	-	-	-	-	6.0	-	1.005	-	-	-
20	-	-	-	-	6.0	-	1.005	-	-	-
21	-	-	-	-	7.5	-	1.000	-	-	-
22	-	-	-	-	7.5	-	1.005	-	-	-
23	-	-	-	-	7.0	-	1.000	-	-	-
24	-	-	-	-	7.0	-	1.005	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

<CONTINUED>

Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 1)										MALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU	
G1 (Vehicle control)											
1	-	-	-	-	6.0	-	≥1.030	-	-	-	
2	-	-	-	-	6.5	-	1.025	-	-	-	
3	-	-	-	-	7.0	-	1.025	-	-	-	
4	-	-	-	-	6.5	-	≥1.030	-	-	-	
5	-	-	-	+	6.5	-	1.010	-	-	-	
6	-	-	-	-	6.5	-	1.025	-	-	-	
G2 (Test article, HADES)											
7	-	-	-	+	6.0	-	≥1.030	-	-	-	
8	-	-	-	-	7.0	-	1.025	-	-	-	
9	-	-	-	1+	6.5	-	≥1.030	-	-	-	
10	-	-	-	-	6.5	-	1.025	-	-	-	
11	-	-	-	-	7.0	-	1.020	-	-	-	
12	-	-	-	-	6.5	-	1.025	-	-	-	

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

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Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 1)									FEMALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
13	-	-	-	+	6.0	-	≥1.030	-	-	-
14	-	-	-	-	6.0	-	1.020	-	-	-
15	-	-	-	-	6.5	-	≥1.030	-	-	-
16	-	-	-	-	7.0	-	≥1.030	-	-	-
17	-	-	-	-	6.5	-	1.020	-	-	-
18	-	-	-	-	7.0	-	1.015	-	-	-
G2 (Test article, HADES)										
19	-	-	-	-	7.0	-	1.015	-	-	-
20	-	-	-	-	7.5	-	1.015	-	-	-
21	-	-	-	+	6.0	-	1.020	-	-	-
22	-	-	-	-	7.5	-	1.010	-	-	-
23	-	-	-	-	7.0	-	1.015	-	-	-
24	-	-	-	+	7.0	-	1.020	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

<CONTINUED>

Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 2)									MALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
1	-	-	-	-	6.0	-	≥1.030	-	-	-
2	-	-	-	+	6.0	-	≥1.030	-	-	-
3	-	-	-	-	7.0	-	1.025	-	-	-
4	-	-	-	-	6.0	-	1.025	-	-	-
5	-	-	-	+	5.0	-	1.025	-	-	-
6	-	-	-	-	7.0	-	1.020	+/-	-	-
G2 (Test article, HADES)										
7	-	-	-	1+	7.0	-	≥1.030	1+	-	-
8	-	-	-	1+	7.0	-	≥1.030	+/-	-	-
9	-	-	-	-	6.5	-	≥1.030	-	-	-
10	-	-	-	-	7.0	-	1.025	-	-	-
11	-	-	-	-	7.0	-	≥1.030	-	-	-
12	-	-	-	-	6.5	-	≥1.030	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

<CONTINUED>

Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 2)									FEMALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
13	-	-	-	+	6.5	-	≥1.030	-	-	-
14	-	-	-	-	6.0	-	≥1.030	-	-	-
15	-	-	-	+	7.0	-	1.025	-	-	-
16	-	-	-	-	6.5	-	≥1.030	-	-	-
17	-	-	-	-	6.0	-	1.020	-	-	-
18	-	-	-	-	7.0	-	1.020	-	-	-
G2 (Test article, HADES)										
19	-	-	-	-	7.0	-	1.005	-	-	-
20	-	-	-	+	8.0	-	1.015	-	-	-
21	-	-	-	-	8.0	-	1.010	-	-	-
22	-	-	-	-	7.0	-	1.025	-	-	-
23	-	-	-	-	6.5	-	≥1.030	-	-	-
24	-	-	-	-	7.0	1+	1.005	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

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Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 3)									MALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
1	-	-	-	+	7.5	-	1.020	-	-	-
2	-	-	-	-	7.0	-	1.015	-	-	-
3	-	-	-	1+	7.5	-	1.025	-	-	-
4	-	-	-	1+	8.0	-	1.015	1+	-	-
5	-	-	-	+	8.0	-	1.015	+	-	-
6	-	-	-	-	7.0	-	1.010	-	-	-
G2 (Test article, HADES)										
7	-	-	-	-	7.5	-	1.010	-	-	-
8	-	-	-	-	7.5	-	1.015	-	-	-
9	-	-	-	+	8.0	-	1.015	-	-	-
10	-	-	-	-	7.0	-	1.015	-	-	-
11	-	-	-	-	7.5	-	1.015	-	-	-
12	-	-	-	+	7.0	-	1.020	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

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Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 3)									FEMALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
13	-	-	-	1+	7.0	-	1.015	-	-	-
14	-	-	-	+	7.0	-	1.015	-	-	-
15	-	-	-	-	6.0	-	1.015	-	-	-
16	-	-	-	+	7.5	-	1.010	-	-	-
17	-	-	-	-	7.0	-	1.010	-	-	-
18	-	-	-	-	6.0	-	1.010	-	-	-
G2 (Test article, HADES)										
19	-	-	-	-	7.5	-	1.005	-	-	-
20	-	-	-	+	7.5	-	1.005	-	-	-
21	-	-	-	+	8.0	-	1.015	-	-	-
22	-	-	-	-	7.5	-	1.015	-	-	-
23	-	-	-	+	8.0	-	1.020	-	-	-
24	-	-	-	+	8.0	-	1.005	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

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Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 4)									MALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
1	-	-	-	+	7.0	-	1.025	+	-	-
2	-	-	-	-	6.5	-	1.020	-	-	-
3	-	-	-	+	6.5	-	1.025	+/-	-	-
4	-	-	-	+	6.0	-	1.025	-	-	-
5	-	-	-	+	6.5	-	1.025	+/-	-	-
6	-	-	-	-	6.5	-	1.020	-	-	-
G2 (Test article, HADES)										
7	-	-	-	+	6.0	-	1.020	-	-	-
8	-	-	-	1+	7.0	-	1.025	+/-	-	-
9	-	-	-	-	6.5	-	1.020	+/-	-	-
10	-	-	-	+	6.5	-	1.025	+	-	-
11	-	-	-	+	6.5	3+	1.020	-	-	-
12	-	-	-	-	6.5	-	1.025	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

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Appendix 4. Individual urinalysis

ANIMAL ID	URINALYSIS (WEEK 4)									FEMALE
	LEU	NIT	URO	PRO	pH	BLO	SG	KET	BIL	GLU
G1 (Vehicle control)										
13	-	-	-	-	7.5	-	1.015	-	-	-
14	-	-	-	-	6.5	-	1.020	-	-	-
15	-	-	-	-	7.0	-	1.005	-	-	-
16	-	-	-	-	6.5	-	1.025	-	-	-
17	-	-	-	-	6.5	-	1.025	-	-	-
18	-	-	-	-	6.5	-	1.015	-	-	-
G2 (Test article, HADES)										
19	-	-	-	-	6.5	-	1.015	-	-	-
20	-	-	-	-	7.0	-	1.010	-	-	-
21	-	-	-	-	6.5	-	1.000	-	-	-
22	-	-	-	-	6.5	-	1.015	-	-	-
23	-	-	-	-	6.5	-	1.015	-	-	-
24	-	-	-	-	6.0	-	1.020	-	-	-

GLU: Glucose, BIL: Bilirubin, KET: Ketone body, SG: Specific gravity, PRO: Protein, URO: Urobilinogen, NIT: Nitrite, BLO: Blood, LEU: Leukocyte.

RESULT	GRADE	GLU (mg/dL)	BIL	KET (mg/dL)	PRO (mg/dL)	URO (EU/dL)	NIT	BLO	LEU
-	0	Negative	Negative	Negative	Negative	0.2	Negative	Negative	Negative
+/-	1	100	NA	5	Trace	1.0	NA	Trace	Trace
+	1	250	NA	15	30	2.4	Positive	NA	NA
1+	2	500	Small	40	100	4.0	NA	10	Small
2+	3	1,000	Moderate	80	300	≥8.0	NA	25	Moderate
3+	4	≥2,000	Large	≥160	≥2000		NA	80	Large

NA: not applicable, SI: slightly.

<END>

Appendix 5. Individual organ weights

ORGAN WEIGHTS (g)							MALE
GROUP: G1 (Vehicle control)							
Animal ID	Testis	Prostate gland	Kidney	Spleen	Lung	Liver	
1	3.465	0.396	2.487	0.726	1.631	10.582	
2	3.797	0.497	2.724	0.701	1.930	10.664	
3	3.177	0.621	2.485	0.721	1.674	10.761	
4	3.977	0.439	3.011	0.897	2.092	11.542	
5	4.227	0.797	2.894	0.759	1.540	11.222	
6	3.537	0.540	2.549	0.786	1.758	12.724	
MEAN	3.697	0.548	2.692	0.765	1.771	11.249	
S.D.	0.379	0.145	0.223	0.071	0.205	0.811	
N	6	6	6	6	6	6	
GROUP: G2 (Test article, HADES)							
Animal ID	Testis	Prostate gland	Kidney	Spleen	Lung	Liver	
7	3.309	0.540	2.705	0.768	1.462	10.160	
8	3.518	0.544	2.530	0.784	1.819	11.226	
9	3.712	0.528	2.728	0.783	1.545	11.512	
10	3.587	0.484	2.663	0.745	1.693	10.945	
11	3.627	0.554	2.873	0.758	1.508	11.442	
12	3.367	0.796	2.817	0.760	1.658	10.596	
MEAN	3.520	0.574	2.719	0.766	1.614	10.980	
S.D.	0.155	0.111	0.120	0.015	0.134	0.525	
N	6	6	6	6	6	6	

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Appendix 5. Individual organ weights

ORGAN WEIGHTS (g)							FEMALE
GROUP: G1 (Vehicle control)							
Animal ID	Ovary	Uterus	Kidney	Spleen	Lung	Liver	
13	0.163	0.979	1.701	0.665	1.161	6.081	
14	0.101	0.428	1.529	0.597	1.414	6.635	
15	0.166	0.407	1.640	0.527	1.373	6.939	
16	0.133	0.975	1.563	0.707	1.608	6.939	
17	0.137	0.976	1.691	0.562	1.254	6.250	
18	0.109	0.806	1.664	0.634	1.381	6.862	
MEAN	0.135	0.762	1.631	0.615	1.365	6.618	
S.D.	0.027	0.275	0.070	0.067	0.152	0.371	
N	6	6	6	6	6	6	
GROUP: G2 (Test article, HADES)							
Animal ID	Ovary	Uterus	Kidney	Spleen	Lung	Liver	
19	0.159	0.769	1.661	0.552	1.118	5.603	
20	0.137	0.418	1.569	0.581	1.468	6.461	
21	0.124	0.500	1.478	0.520	1.283	5.986	
22	0.151	0.583	1.750	0.655	1.366	7.161	
23	0.152	0.802	1.755	0.920	1.146	6.540	
24	0.142	1.113	1.620	0.636	1.150	6.681	
MEAN	0.144	0.698	1.639	0.644	1.255	6.405	
S.D.	0.013	0.253	0.107	0.144	0.142	0.545	
N	6	6	6	6	6	6	

<END>

Appendix 6. Hematological test

		HEMATOLOGICAL TEST						MALE	
GROUP		G1 (Vehicle control)							
TESTS	UNITS	1	2	3	4	5	6	MEAN	S.D.
WBCB	10 ³ /μL	8.30	6.21	9.91	7.17	8.05	7.55	7.87	1.24
RBC	10 ⁶ /μL	8.75	8.37	8.31	8.68	8.94	8.28	8.56	0.27
HGB	g/dL	16.10	15.40	14.80	15.40	15.60	15.40	15.45	0.42
HCT	%	49.30	48.10	45.80	47.70	48.40	47.90	47.87	1.16
MCV	fL	56.30	57.50	55.20	55.00	54.20	57.80	56.00	1.45
MCH	pg	18.40	18.40	17.80	17.70	17.50	18.60	18.07	0.45
MCHC	g/dL	32.60	32.00	32.20	32.20	32.30	32.10	32.23	0.21
RDW	%	12.10	11.60	12.30	11.60	11.30	11.50	11.73	0.38
HDW	g/dL	2.64	2.39	2.45	2.59	2.30	2.47	2.47	0.13
PLT	10 ³ /μL	1072.00	1057.00	1201.00	1219.00	1276.00	1228.00	1175.50	89.61
MPV	fL	6.30	6.90	6.70	6.60	6.80	6.50	6.63	0.22
NEUT	%	9.00	11.00	11.90	25.40	8.60	10.00	12.65	6.37
LYM	%	82.00	84.30	84.90	70.30	88.40	86.40	82.72	6.45
MONO	%	2.20	3.30	1.50	3.20	1.70	2.60	2.42	0.75
EOS	%	3.90	0.50	0.70	0.30	0.40	0.20	1.00	1.43
BASO	%	0.10	0.20	0.20	0.10	0.20	0.20	0.17	0.05
LUC	%	2.80	0.70	0.80	0.60	0.70	0.50	1.02	0.88
NEUT	10 ³ /μL	0.75	0.68	1.18	1.82	0.69	0.75	0.98	0.45
LYM	10 ³ /μL	6.81	5.23	8.41	5.05	7.11	6.52	6.52	1.25
MONO	10 ³ /μL	0.18	0.20	0.15	0.23	0.14	0.20	0.18	0.03
EOS	10 ³ /μL	0.33	0.03	0.07	0.02	0.03	0.02	0.08	0.12
LUC	10 ³ /μL	0.23	0.04	0.08	0.04	0.06	0.04	0.08	0.07
BASO	10 ³ /μL	0.01	0.01	0.02	0.01	0.02	0.02	0.02	0.01
RET	%	2.84	3.39	3.00	3.06	2.67	3.52	3.08	0.32

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Appendix 6. Hematological test

		HEMATOLOGICAL TEST						MALE	
GROUP		G2 (Test article, HADES)							
TESTS	UNITS	7	8	9	10	11	12	MEAN	S.D.
WBCB	10 ³ /μL	8.48	8.29	7.54	5.75	8.14	6.29	7.42	1.14
RBC	10 ⁶ /μL	7.97	8.38	8.57	8.25	8.26	9.03	8.41	0.36
HGB	g/dL	15.20	15.00	15.40	15.90	15.40	15.70	15.43	0.33
HCT	%	46.80	46.60	47.90	48.00	47.60	48.40	47.55	0.71
MCV	fL	58.70	55.60	55.80	58.20	57.60	53.60	56.58	1.93
MCH	pg	19.10	17.80	18.00	19.20	18.70	17.40	18.37	0.74
MCHC	g/dL	32.50	32.10	32.20	33.00	32.40	32.40	32.43	0.31
RDW	%	11.60	12.10	11.90	11.30	11.30	11.60	11.63	0.32
HDW	g/dL	2.41	2.46	2.47	2.26	2.28	2.35	2.37	0.09
PLT	10 ³ /μL	1203.00	1238.00	1145.00	1268.00	1203.00	1068.00	1187.50	71.55
MPV	fL	6.80	6.70	6.50	6.30	6.70	6.80	6.63	0.20
NEUT	%	17.40	12.10	14.90	12.10	18.00	11.30	14.30	2.91
LYM	%	77.90	84.20	81.50	83.40	79.20	85.00	81.87	2.85
MONO	%	2.90	2.20	2.20	2.50	1.60	2.40	2.30	0.43
EOS	%	0.70	0.30	0.30	0.60	0.50	0.60	0.50	0.17
BASO	%	0.20	0.30	0.10	0.30	0.20	0.10	0.20	0.09
LUC	%	1.00	0.90	1.00	1.10	0.50	0.70	0.87	0.23
NEUT	10 ³ /μL	1.47	1.01	1.12	0.70	1.46	0.71	1.08	0.34
LYM	10 ³ /μL	6.60	6.98	6.15	4.79	6.45	5.35	6.05	0.83
MONO	10 ³ /μL	0.25	0.18	0.16	0.14	0.13	0.15	0.17	0.04
EOS	10 ³ /μL	0.06	0.03	0.03	0.04	0.04	0.04	0.04	0.01
LUC	10 ³ /μL	0.08	0.07	0.07	0.06	0.04	0.04	0.06	0.02
BASO	10 ³ /μL	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01
RET	%	3.14	3.21	3.01	2.40	2.72	2.75	2.87	0.31

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Appendix 6. Hematological test

		HEMATOLOGICAL TEST						FEMALE	
GROUP		G1 (Vehicle control)							
TESTS	UNITS	13	14	15	16	17	18	MEAN	S.D.
WBCB	10 ³ /μL	2.58	3.80	3.86	3.96	3.73	3.61	3.59	0.51
RBC	10 ⁶ /μL	7.89	8.55	8.39	7.99	7.98	8.41	8.20	0.28
HGB	g/dL	14.50	15.40	14.80	14.40	14.60	14.90	14.77	0.36
HCT	%	43.60	45.60	45.60	44.10	44.10	44.60	44.60	0.84
MCV	fL	55.20	53.40	54.40	55.20	55.20	53.00	54.40	0.99
MCH	pg	18.40	18.00	17.70	18.10	18.30	17.70	18.03	0.29
MCHC	g/dL	33.30	33.80	32.60	32.70	33.20	33.40	33.17	0.45
RDW	%	11.00	10.70	10.80	11.40	11.00	10.60	10.92	0.29
HDW	g/dL	2.21	2.29	2.18	2.38	2.29	2.22	2.26	0.07
PLT	10 ³ /μL	774.00	1254.00	1187.00	1180.00	1068.00	1131.00	1099.00	170.84
MPV	fL	7.60	6.70	6.50	6.50	6.70	6.70	6.78	0.41
NEUT	%	12.70	10.40	22.70	28.10	14.80	11.70	16.73	7.07
LYM	%	84.60	84.70	74.10	67.60	81.00	84.50	79.42	7.09
MONO	%	1.80	2.80	2.10	2.70	2.60	2.60	2.43	0.39
EOS	%	0.40	1.20	0.50	1.00	0.90	0.50	0.75	0.33
BASO	%	0.00	0.10	0.20	0.10	0.10	0.10	0.10	0.06
LUC	%	0.40	0.90	0.30	0.50	0.60	0.60	0.55	0.21
NEUT	10 ³ /μL	0.33	0.40	0.88	1.11	0.55	0.42	0.62	0.31
LYM	10 ³ /μL	2.18	3.22	2.86	2.68	3.02	3.05	2.84	0.37
MONO	10 ³ /μL	0.05	0.11	0.08	0.11	0.10	0.09	0.09	0.02
EOS	10 ³ /μL	0.01	0.04	0.02	0.04	0.03	0.02	0.03	0.01
LUC	10 ³ /μL	0.01	0.03	0.01	0.02	0.02	0.02	0.02	0.01
BASO	10 ³ /μL	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
RET	%	2.93	2.22	3.03	3.62	3.13	2.84	2.96	0.45

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Appendix 6. Hematological test

		HEMATOLOGICAL TEST						FEMALE	
GROUP		G2 (Test article, HADES)							
TESTS	UNITS	19	20	21	22	23	24	MEAN	S.D.
WBCB	10 ³ /μL	2.90	3.45	3.14	5.51	4.15	3.03	3.70	0.99
RBC	10 ⁶ /μL	8.38	7.80	8.14	8.32	8.28	8.09	8.17	0.21
HGB	g/dL	14.50	14.50	14.80	14.70	15.00	14.90	14.73	0.21
HCT	%	43.90	43.90	45.10	44.00	45.10	45.20	44.53	0.66
MCV	fL	52.40	56.30	55.30	52.90	54.50	55.80	54.53	1.58
MCH	pg	17.30	18.60	18.20	17.60	18.10	18.50	18.05	0.51
MCHC	g/dL	33.10	33.00	32.90	33.40	33.20	33.10	33.12	0.17
RDW	%	11.90	10.90	11.00	11.40	11.50	11.00	11.28	0.39
HDW	g/dL	2.58	2.20	2.19	2.32	2.52	2.36	2.36	0.16
PLT	10 ³ /μL	692.00	1209.00	1166.00	1299.00	768.00	1020.00	1025.67	247.29
MPV	fL	7.60	7.10	7.20	6.70	7.40	6.40	7.07	0.45
NEUT	%	10.00	20.50	16.40	16.00	6.90	14.00	13.97	4.87
LYM	%	86.00	73.40	79.90	80.80	90.00	81.00	81.85	5.67
MONO	%	2.70	4.20	1.60	2.00	2.10	3.00	2.60	0.93
EOS	%	0.50	1.30	1.40	0.50	0.40	1.00	0.85	0.44
BASO	%	0.10	0.10	0.20	0.20	0.10	0.20	0.15	0.05
LUC	%	0.60	0.60	0.60	0.60	0.60	0.90	0.65	0.12
NEUT	10 ³ /μL	0.29	0.71	0.52	0.88	0.28	0.42	0.52	0.24
LYM	10 ³ /μL	2.50	2.53	2.51	4.45	3.73	2.45	3.03	0.85
MONO	10 ³ /μL	0.08	0.14	0.05	0.11	0.09	0.09	0.09	0.03
EOS	10 ³ /μL	0.01	0.04	0.04	0.03	0.02	0.03	0.03	0.01
LUC	10 ³ /μL	0.02	0.02	0.02	0.03	0.02	0.03	0.02	0.01
BASO	10 ³ /μL	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00
RET	%	2.97	3.37	2.47	2.78	3.05	2.87	2.92	0.30

<END>

Appendix 7. Clinical biochemistry test

GROUP		CLINICAL BIOCHEMISTRY TEST						MALE	
TESTS	UNITS	G1 (Vehicle control)						MEAN	S.D.
		1	2	3	4	5	6		
AST	U/L	142.40	163.00	137.80	136.10	145.30	158.10	147.12	11.01
ALT	U/L	32.50	24.70	30.00	29.40	28.80	26.70	28.68	2.71
ALP	U/L	127.50	179.00	171.10	149.00	141.60	156.70	154.15	19.00
CPK	U/L	718.00	880.00	641.00	705.00	779.00	998.00	786.83	131.18
TBIL	mg/dL	0.11	0.11	0.12	0.12	0.12	0.13	0.12	0.01
GLU	mg/dL	128.20	146.60	109.30	110.10	101.00	122.80	119.67	16.46
TCHO	mg/dL	83.00	93.00	69.00	81.00	67.00	79.00	78.67	9.58
TG	mg/dL	49.00	34.00	41.00	37.00	41.00	46.00	41.33	5.54
TP	g/dL	6.04	5.79	5.82	6.03	5.92	5.98	5.93	0.11
ALB	g/dL	3.18	3.03	3.09	3.09	3.10	3.20	3.12	0.06
A/G ratio		1.11	1.10	1.13	1.05	1.10	1.15	1.11	0.03
BUN	mg/dL	13.90	14.50	13.10	13.60	13.30	12.90	13.55	0.59
CRE	mg/dL	0.39	0.43	0.39	0.40	0.40	0.42	0.41	0.02
IP	mg/dL	8.80	9.19	8.58	8.97	8.87	8.80	8.87	0.20
Ca ²⁺	mg/dL	9.26	9.18	9.38	9.37	9.36	9.40	9.33	0.09
Na ⁺	mmol/L	141.71	142.96	144.69	143.85	142.82	141.99	143.00	1.12
K ⁺	mmol/L	4.46	4.36	4.51	4.63	4.66	4.53	4.53	0.11
Cl ⁻	mmol/L	98.89	98.52	101.29	99.57	98.92	100.15	99.56	1.03

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Appendix 7. Clinical biochemistry test

GROUP		CLINICAL BIOCHEMISTRY TEST						MALE	
TESTS	UNITS	G2 (Test article, HADES)						MEAN	S.D.
		7	8	9	10	11	12		
AST	U/L	132.70	141.60	140.10	112.50	142.40	110.20	129.92	14.80
ALT	U/L	30.10	30.70	25.00	28.70	33.60	28.90	29.50	2.82
ALP	U/L	205.90	129.90	116.40	201.40	127.00	155.80	156.07	39.09
CPK	U/L	753.00	809.00	812.00	609.00	683.00	472.00	689.67	132.02
TBIL	mg/dL	0.13	0.12	0.12	0.13	0.13	0.11	0.12	0.01
GLU	mg/dL	113.80	110.00	125.30	119.60	108.80	107.70	114.20	6.95
TCHO	mg/dL	87.00	71.00	68.00	86.00	68.00	68.00	74.67	9.24
TG	mg/dL	49.00	43.00	58.00	59.00	56.00	40.00	50.83	8.08
TP	g/dL	6.16	6.00	6.13	5.96	5.90	5.75	5.98	0.15
ALB	g/dL	3.26	3.25	3.22	3.18	3.12	3.05	3.18	0.08
A/G ratio		1.12	1.18	1.11	1.14	1.12	1.13	1.13	0.03
BUN	mg/dL	12.80	13.70	13.50	14.80	14.10	14.70	13.93	0.76
CRE	mg/dL	0.39	0.46	0.42	0.41	0.38	0.42	0.41	0.03
IP	mg/dL	8.31	9.20	8.84	8.45	8.69	9.26	8.79	0.39
Ca ²⁺	mg/dL	9.25	9.60	9.54	9.48	9.57	9.52	9.49	0.13
Na ⁺	mmol/L	144.55	143.94	144.27	143.10	143.66	143.85	143.90	0.50
K ⁺	mmol/L	4.26	4.58	4.63	4.49	4.32	4.75	4.51	0.19
Cl ⁻	mmol/L	100.94	100.91	98.69	99.91	99.67	100.32	100.07	0.85

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Appendix 7. Clinical biochemistry test

GROUP		CLINICAL BIOCHEMISTRY TEST						FEMALE	
TESTS	UNITS	G1 (Vehicle control)						MEAN	S.D.
		13	14	15	16	17	18		
AST	U/L	108.30	125.20	109.20	127.40	109.90	129.10	118.18	10.00
ALT	U/L	25.10	24.60	22.10	22.60	27.80	28.10	25.05	2.52
ALP	U/L	81.90	88.00	115.70	89.40	113.50	84.80	95.55	15.00
CPK	U/L	285.00	520.00	412.00	503.00	349.00	558.00	437.83	107.10
TBIL	mg/dL	0.11	0.14	0.16	0.15	0.17	0.15	0.15	0.02
GLU	mg/dL	95.10	105.30	96.00	83.60	93.70	98.30	95.33	7.06
TCHO	mg/dL	68.00	124.00	61.00	102.00	83.00	87.00	87.50	23.00
TG	mg/dL	27.00	30.00	34.00	43.00	31.00	38.00	33.83	5.85
TP	g/dL	5.64	5.56	6.06	5.68	5.66	5.53	5.69	0.19
ALB	g/dL	3.12	3.09	3.29	2.93	3.16	3.02	3.10	0.12
A/G ratio		1.24	1.25	1.19	1.07	1.26	1.20	1.20	0.07
BUN	mg/dL	16.20	16.40	15.00	19.10	16.90	16.80	16.73	1.34
CRE	mg/dL	0.49	0.36	0.45	0.45	0.44	0.42	0.44	0.04
IP	mg/dL	6.74	7.58	6.84	7.12	6.64	7.53	7.08	0.41
Ca ²⁺	mg/dL	9.04	9.39	9.10	9.39	9.31	9.19	9.24	0.15
Na ⁺	mmol/L	143.89	142.36	142.91	142.26	142.22	141.99	142.61	0.70
K ⁺	mmol/L	3.95	4.45	3.88	4.00	4.10	4.26	4.11	0.21
Cl ⁻	mmol/L	103.47	102.37	102.34	102.55	102.83	101.19	102.46	0.75

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Appendix 7. Clinical biochemistry test

GROUP		CLINICAL BIOCHEMISTRY TEST						FEMALE	
TESTS	UNITS	G2 (Test article, HADES)						MEAN	S.D.
		19	20	21	22	23	24		
AST	U/L	108.70	110.30	99.80	102.30	94.90	107.00	103.83	5.90
ALT	U/L	27.80	20.20	25.40	24.80	23.30	24.60	24.35	2.51
ALP	U/L	112.60	114.50	94.50	132.00	104.80	88.00	107.73	15.69
CPK	U/L	169.00	320.00	200.00	248.00	168.00	317.00	237.00	69.52
TBIL	mg/dL	0.13	0.16	0.13	0.17	0.14	0.14	0.15	0.02
GLU	mg/dL	98.80	96.10	106.70	95.70	94.10	107.00	99.73	5.72
TCHO	mg/dL	63.00	72.00	68.00	85.00	60.00	79.00	71.17	9.54
TG	mg/dL	33.00	34.00	27.00	31.00	31.00	34.00	31.67	2.66
TP	g/dL	5.61	6.13	5.65	5.81	5.93	5.53	5.78	0.23
ALB	g/dL	3.19	3.39	3.21	3.15	3.29	3.03	3.21	0.12
A/G ratio		1.32	1.24	1.32	1.18	1.25	1.21	1.25	0.06
BUN	mg/dL	18.20	18.40	15.10	16.70	18.50	18.70	17.60	1.42
CRE	mg/dL	0.49	0.52	0.46	0.41	0.46	0.46	0.47	0.04
IP	mg/dL	5.23	7.15	7.79	7.46	6.77	7.55	6.99	0.93
Ca ²⁺	mg/dL	8.80	9.44	9.20	9.42	9.34	9.40	9.27	0.24
Na ⁺	mmol/L	144.50	142.08	142.87	141.62	142.96	142.50	142.76	0.99
K ⁺	mmol/L	3.77	3.99	5.28	4.35	3.92	4.39	4.28	0.55
Cl ⁻	mmol/L	105.54	103.11	104.32	102.48	103.32	104.36	103.86	1.10

<END>

Appendix 8. Individual Scoring Data of Each Lesion

Organ / Histopathology	1	2	3	4	5	6
Nasal cavity	NSL	NSL	NSL	NSL	NSL	NSL
Trachea	NSL	NSL	NSL	NSL	NSL	NSL
Cell infiltration, lymphocytic, LP & submucosa						
Lung	NSL		NSL	NSL	NSL	NSL
Inflammatory foci, chronic		1+				
Cell infiltration, lymphoid cells, perivascular						
Hemoglobin pneumonia, focal						
Liver	NSL	NSL	NSL	NSL	NSL	NSL
Cell infiltration, mononuclear cell, (multi)focal						
Metastatic tumor cells, focal						
Kidney		NSL	NSL			NSL
Focal nephropathy, (multi)focal				1+		
Basophilic tubules, (multi)focal	1+				1+	
Mineralization, (multi)focal	1+					
Spleen	NSL	NSL	NSL	NSL	NSL	NSL
Mononuclear cell leukemia						
Testis	NSL	NSL	NSL	NSL	NSL	NSL
Epididymis	NSL	NSL	NSL	NSL	NSL	NSL
Prostate gland	NSL	NSL	NSL			NSL
Lymphoid cell infiltration, interstitium				1+	1+	
Eyes	NSL	NSL	NSL	NSL	NSL	NSL

NSL, No specific lesion;

Grades: 1+, minimal; 2+, mild; 3+, moderate; 4+, severe

<CONTINUED>

Appendix 8. Individual Scoring Data of Each Lesion

Organ / Histopathology	7	8	9	10	11	12
Nasal cavity	NSL	NSL	NSL	NSL	NSL	NSL
Trachea		NSL	NSL	NSL	NSL	NSL
Cell infiltration, lymphocytic, LP & submucosa	1+					
Lung	NSL	NSL	NSL	NSL	NSL	NSL
Inflammatory foci, chronic						
Cell infiltration, lymphoid cells, perivascular						
Hemoglobin pneumonia, focal						
Liver	NSL	NSL	NSL	NSL	NSL	NSL
Cell infiltration, mononuclear cell, (multi)focal						
Metastatic tumor cells, focal						
Kidney	NSL	NSL	NSL	NSL	NSL	NSL
Focal nephropathy, (multi)focal						
Basophilic tubules, (multi)focal						
Mineralization, (multi)focal						
Spleen	NSL	NSL	NSL	NSL	NSL	NSL
Mononuclear cell leukemia						
Testis	NSL	NSL	NSL	NSL	NSL	NSL
Epididymis	NSL	NSL	NSL	NSL	NSL	NSL
Prostate gland	NSL		NSL	NSL	NSL	NSL
Lymphoid cell infiltration, interstitium		1+				
Eyes	NSL	NSL	NSL	NSL	NSL	NSL

NSL, No specific lesion;

Grades: 1+, minimal; 2+, mild; 3+, moderate; 4+, severe

<CONTINUED>

Appendix 8. Individual Scoring Data of Each Lesion

Organ / Histopathology	13	14	15	16	17	18
Nasal cavity	NSL	NSL	NSL	NSL	NSL	NSL
Trachea	NSL	NSL	NSL	NSL		NSL
Cell infiltration, lymphocytic, LP & submucosa					1+	
Lung	NSL	NSL	NSL	NSL		NSL
Inflammatory foci, chronic					1+	
Cell infiltration, lymphoid cells, perivascular					1+	
Hemoglobin pneumonia, focal						
Liver	NSL	NSL	NSL	NSL		NSL
Cell infiltration, mononuclear cell, (multi)focal					1+	
Metastatic tumor cells, focal						
Kidney	NSL	NSL	NSL	NSL	NSL	NSL
Focal nephropathy, (multi)focal						
Basophilic tubules, (multi)focal						
Mineralization, (multi)focal						
Spleen	NSL	NSL	NSL	NSL	NSL	NSL
Mononuclear cell leukemia						
Ovary	NSL	NSL	NSL	NSL	NSL	NSL
Uterus		NSL	NSL			
Hydrometra, unilateral or bilateral	P(3+)			P(3+)	P(3+)	P(3+)
Eyes	NSL	NSL	NSL	NSL	NSL	NSL

NSL, No specific lesion;

Grades: 1+, minimal; 2+, mild; 3+, moderate; 4+, severe

<CONTINUED>

Appendix 8. Individual Scoring Data of Each Lesion

Organ / Histopathology	19	20	21	22	23	24
Nasal cavity	NSL	NSL	NSL	NSL	NSL	NSL
Trachea	NSL	NSL	NSL	NSL	NSL	NSL
Cell infiltration, lymphocytic, LP & submucosa						
Lung	NSL	NSL	NSL	NSL	NSL	NSL
Inflammatory foci, chronic						
Cell infiltration, lymphoid cells, perivascular						
Hemoglobin pneumonia, focal						
Liver	NSL	NSL	NSL	NSL		NSL
Cell infiltration, mononuclear cell, (multi)focal						
Metastatic tumor cells, focal					P(1+)	
Kidney	NSL	NSL	NSL	NSL	NSL	
Focal nephropathy, (multi)focal						
Basophilic tubules, (multi)focal						
Mineralization, (multi)focal						1+
Spleen	NSL	NSL	NSL	NSL		NSL
Mononuclear cell leukemia					P(3+)	
Ovary	NSL	NSL	NSL	NSL	NSL	NSL
Uterus	NSL	NSL	NSL			
Hydrometra, unilateral or bilateral				P(3+)	P(3+)	P(3+)
Eyes	NSL	NSL	NSL	NSL	NSL	NSL

NSL, No specific lesion;

Grades: 1+, minimal; 2+, mild; 3+, moderate; 4+, severe

<END>