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Additives

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Via Federal Express

May 11, 1999

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Document Control Office (7407)
Room G99 East Tower
Attention: Section 8(e)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460-0001

Subject: TSCA 8(e) Notice - FS 042 (TKA 40082)

Dear Section 8(e) Coordinator:

This letter and enclosed report do not contain Confidential Business Information.

In accordance with EPA's March 16, 1978 Policy Statement on Section 8(e) reporting under the Toxic Substances Control Act (TSCA), the EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba Specialty Chemicals Corporation wishes to bring to the attention of the Environmental Protection Agency results observed in a 90-day dog study conducted with TKA 40082 (FS 042). FS 042, a commercial polymer stabilizer, is amines, bis(hydrogenated tallow alkyl), oxidized; CASRN 143925-92-2.

We are enclosing a copy of the study entitled, ***" 90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs"***. This study was conducted with male and female Beagle dogs at doses of 0, 10, 50, 200, and 1,000 mg/Kg/day. There were no chemical-related effects on behavior, body weights, organ weights, or food consumption; ophthalmological examinations were also negative. However, at the highest dose level (1,000 mg/Kg/day) hepatocellular degeneration, necrosis and inflammation was observed which correlated with elevated alanine aminotransferase levels in blood serum. The NOEL was 200 mg/Kg/day.

Based upon current EPA guidelines, it is felt these results warrant reporting under TSCA 8(e). Please call the undersigned if you have any questions concerning this submittal.

Respectfully,

Ciba Specialty Chemicals Corporation

Thomas Barber, Manager
Product Registration and Compliance

Contains No CBI

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Tarrytown, NY 10591-9005

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Value beyond chemistry

Final Report

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Contains No CBI

PREPARED FOR:
Additives Division
Ciba Specialty Chemicals Corporation

COVANCE STUDY NUMBER:
6623-117

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Sponsor:

Additives Division
Ciba Specialty Chemicals Corporation
540 White Plains Road
P.O. Box 2005
Tarrytown, New York 10591-9005

FINAL REPORT

Study Title:

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Author:

Marie E. McKeon, MPhil, DABT

Study Completion Date:

April 30, 1999

Performing Laboratory:

Covance Laboratories Inc.
9200 Leesburg Pike
Vienna, Virginia 22182-1699

Laboratory Study Identification:

Covance 6623-117

COMPLIANCE STATEMENT

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

This study, as performed by Covance Laboratories Inc., was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and in the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice C(97)186 (Final) (November 26. 1997), and with any applicable amendments.

Marie E. McKeon

Marie E. McKeon, MPhil, DABT
Study Director

April 30, 1999
Date

QUALITY ASSURANCE STATEMENT

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Quality Assurance inspections and reviews of this study were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the Good Laboratory Practice regulations of the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979) and with any applicable amendments, and with the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice C(97)186 (Final) (November 26, 1997). These inspections and reviews were performed and findings were reported to the Study Director and management as follows:

Dates of Inspection/Review	Dates Findings Reported	Inspector/Reviewer
Protocol Review:		
07/24/98	07/24/98	M. Hincy
Inspection and/or Data Review:		
08/06/98	08/06/98	M. Hincy
10/12-14,16/98	10/16/98	S. Godfrey/ N. Strickland
11/06/98	11/06/98	D. Bland/ N. Strickland
11/16,17/98	11/19/98	L. Cassell/ N. Strickland
Report and Data Review:		
02/5,8-9,11,12,15/99	02/15/99	S. Godfrey/ N. Strickland
04/28/99	04/28/99	D. Bland

D Bland 4-30-99

Desireé D. Bland — Date Released

Quality Assurance Unit

STUDY IDENTIFICATION

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Covance Study No.:	6623-117
Test Material:	TKA 40082
Study Monitor:	Richard Balcomb
Sponsor:	Additives Division Ciba Specialty Chemicals Corporation 540 White Plains Road P.O. Box 2005 Tarrytown, New York 10591-9005 (914) 785-4496
Study Director:	Marie E. McKeon, MPhil, DABT Covance Laboratories Inc. 9200 Leesburg Pike Vienna, Virginia 22182-1699 (703) 893-5400
Study Timetable	
Study Initiation:	July 16, 1998
In-life Start Date:	August 5, 1998
In-life End Date:	November 9, 1998
Study Completion Date:	April 30, 1999

KEY PERSONNEL

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Study Director:	Marie E. McKeon, MPhil, DABT
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Anatomical Pathologist:	Ricardo V. Quander, DVM, Diplomate, ACVP
Dose Formulations Supervisor:	William Caparoon, AA
Toxicology Operations Supervisor:	Charles F. Hatcher, BS, LAT
Postlife and Clinical Pathology Laboratories Supervisor:	Kelly Bell, BS

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ABSTRACT

The purpose of the study was to evaluate the toxicity of TKA 40082 when administered daily by capsule to dogs for at least 90 days.

Male and female purebred beagle dogs were assigned to five groups (four/sex/group). Each group received 0, 10, 50, 200, 1000 mg of TKA 40082 per kg of body weight (mg/kg) per dose via capsule daily for at least 90 days. The daily dose was divided in half (0, 5, 25, 100, and 500 mg/kg/dose) and delivered 4 to 5 hours apart. Control dogs received the same size and number of capsules as the high-dose dogs at each dosing period (two).

Diet and water were provided *ad libitum*, except when animals were fasted for blood collection. The animals were observed twice daily (a.m. and p.m.) for mortality and moribundity. At least once daily, animals were examined for abnormalities and signs of toxicity. Body weights and food consumption data were collected weekly. A thorough physical examination was conducted at each weighing interval. Ophthalmic examinations were done before initiation of treatment and prior to scheduled sacrifice. Blood and urine samples were collected for clinical hematology, clinical chemistry, and urinalysis tests once before initiation of treatment and during Weeks 8 and 13. After 90 days of treatment, the animals were weighed, anesthetized, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, selected organs were weighed, and selected tissues were collected and preserved. Microscopic examinations were done on tissues from each animal in the control and high-dose groups.

There were no toxicologically relevant test article-related effects on clinical observations, body weights, food consumption, or ophthalmological examinations. At necropsy, observations were typical of beagle dogs of this age. Microscopic changes consisting of hepatocellular degeneration and necrosis and in increased severity of hepatic inflammation were present in the livers of dogs which received 1000 mg/kg/day. These liver findings correlated with elevations in alanine aminotransferase in these dogs. Based upon the histological findings and elevated alanine aminotransferase levels at 1000 mg/kg/day, the no-observable-effect level (NOEL) for TKA 40082 is 200 mg/kg/day when divided evenly over two daily capsule doses for at least 90 days.

PURPOSE

This study was designed to evaluate the toxicity of TKA 40082 when administered daily by capsule to dogs for at least 90 days.

REGULATORY COMPLIANCE

The study, as performed by Covance, was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and in the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice C(97)186 (Final) (November 26, 1997), and with any applicable amendments.

The protocol was reviewed and approved by the Institutional Animal Care and Use Committee at Covance.

TEST AND CONTROL MATERIALS

Test Material

The test material, TKA 40082, Batch No. 980426042 (expiration April 29, 2001), was received from the Sponsor on June 22, 1998, and stored at room temperature, protected from light. It was described as a white to off-white powder. The reported quantified active content of test material was 94.9%[a]; no adjustment was made.

Information on synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor.

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[a]Certificate of Analysis (Title: Characterization and Purity Determination of CGA-042 Batch # 980426042) provided by the Sponsor and maintained in the raw data.

Control Material

Clear, empty, size 11, capsules, Batch No. 675 (expiration date: May 2003), were received from Torpac, Inc., Fairfield, New Jersey, on May 27, 1998, and used as the vehicle for oral administration of the test material and as the control material. Information on synthesis methods, composition, or other characteristics that define the control material is on file with the manufacturer.

Reserve (Archive) Samples

A sample of each lot of the test (5 g) and control (one capsule) materials was taken and stored at room temperature, protected from light. These samples were archived by Covance after completion of the in-life phase. Residual test material was returned to the Sponsor on November 17, 1998.

TEST ANIMALS AND HUSBANDRY

Animals. Forty (20/sex) purebred beagle dogs were selected for this study based on pretreatment physical examinations, ophthalmic examinations, and clinical laboratory tests.

The dogs were received on July 23, 1998, from Covance Research Products, Inc., Cumberland, Virginia. All dogs were vaccinated against distemper, hepatitis, leptospirosis, parainfluenza, parvovirus, and rabies and uniquely identified by supplier-applied ear tattoos. They were acclimated for 12 days[a] prior to the initiation of dosing.

Housing. Each dog was individually housed in an elevated, stainless-steel cage measuring 90 x 83 x 79 cm (d x w x h) and assigned a temporary number that was used as identification during the pretreatment evaluations and randomization.

Diet. Certified canine diet (#8727C, Harlan Teklad), was available *ad libitum* during the acclimation and study periods, unless otherwise noted. The diet was analyzed by the

[a] See Appendix of Protocol Deviations.

manufacturer for nutritional components and environmental contaminants. (Specified nutrient and contaminant analyses are on file at Covance-Vienna.)

Water. Tap water was available *ad libitum*. Samples of the water are routinely analyzed for specified microorganisms and environmental contaminants.

Contaminants. Results of the diet and water analyses are reviewed for compliance and are on file at Covance-Vienna.

No contaminants were known to be present in the diet or water at levels which might interfere with this study.

Environmental Conditions. The temperature and relative humidity in the animal room were set to maintain the protocol range of 18 to 29°C (64 to 84°F), with a relative humidity of 50 ± 20%. During the study period, they were monitored at least once daily. Deviations from these ranges are maintained in the raw data and are not believed to have had an effect on the outcome of the study. Ten or greater air changes/hour and a 12-hour light/12-hour dark cycle (0600 to 1800 hours light/1800 to 0600 hours dark) were maintained.

Exercise. The dogs were exercised in accordance with Covance-Vienna SOP No. 1,751.0 for complying with the Animal Welfare Act and its modifications.

Justification of Species. The dog historically has been used in safety evaluation studies and is recommended by appropriate regulatory agencies.

METHODS

This study was conducted in accordance with Covance Protocol 6623-117 dated July 16, 1998, and any protocol amendments. The protocol, protocol amendments, and protocol deviations are presented in Appendix 1.

Group Designations and Dose Levels

The dogs used on this study were stratified by weight and randomly assigned to the groups using a computer-generated randomization program. The dogs were assigned to the groups as follows:

Group	Dosage Level		Number of Animals		Animal Numbers	
	mg/kg/day	mg/kg/dose	Male	Female	Male	Female
1 (Control)	0	0	4	4	G35543-G35546	G35547-G35550
2 (Low)	10	5	4	4	G35551-G35554	G35555-G35558
3 (Mid)	50	25	4	4	G35559-G35562	G35563-G35566
4 (Mid-High)	200	100	4	4	G35567-G35570	G35571-G35574
5 (High)	1000	500	4	4	G35575-G35578	G35579-G35582

Following randomization, each animal was uniquely identified by a permanent number in the form of an implantable microchip identification device inserted subcutaneously into the scapular region. The microidentification implant system, in conjunction with a computerized data capture system, allows for on-line electronic identification of individual animals and collection of data.

At initiation of dosing, the animals were approximately 7 months old,[a] with body weights ranging from 7.9 to 10.1 kg for the males and 7.4 to 10.1 kg for the females.

Reason for Dosing Route. The test material was delivered twice daily by capsule to simulate dietary exposure.

DOSING PROCEDURES

Dose Preparation

Dosing formulations were prepared at least once weekly. Capsule preparation was based on the test material as supplied. The required amount of TKA 40082 for each dog was weighed on an appropriate balance, and the test material weight, weigh date, and project,

[a] See Appendix of Protocol Deviations.

week, group, and dog numbers were recorded electronically on tape. The test material was transferred to ½-oz capsules which were placed in appropriately labeled vials; the vials were placed in opaque containers to protect the test material from light. All formulations were stored at room temperature until dispensed to the animal laboratory. The daily amount of test material for each animal was based on the most recently recorded body weight.

Method of Administration

Doses were administered twice daily, 4 to 5 hours apart, for at least 90 days. The daily dose was divided in half. Dosages were based on the most recently recorded body weight. Treatment for each animal continued through the day before its scheduled necropsy. Control dogs received the same size and number of capsules at each dose as the high-dose animals. Two capsules per dose were needed to accommodate the bulk of the test material for the high-dose dogs.

Dose Analyses

Since the test material was not mixed with a carrier, analyses were not required.

ANTEMORTEM PROCEDURES

Observation of Animals

Clinical Observations. All dogs were observed twice daily (a.m. and p.m., at least 6 hours between observations) for evidence of mortality and moribundity and once daily at the time of the afternoon mortality check for evidence of toxic or pharmacologic effect. A thorough weekly physical examination was conducted at each weighing interval.

Body Weights. Body weights were recorded at least once prior to treatment (maintained in the raw data), on the first day of treatment, and weekly thereafter.

Food Consumption. Food consumption was recorded weekly.

Ophthalmic Examinations. Ophthalmic examinations were performed prior to treatment and prior to scheduled sacrifice using an indirect ophthalmoscope. A mydriatic solution was used for pupil dilation.

Clinical Pathology

At least once prior to treatment and during Weeks 8 and 13, the following clinical pathology tests were performed:

Hematology

red blood cell (erythrocyte) count
hemoglobin
hematocrit
mean corpuscular volume
mean corpuscular hemoglobin
mean corpuscular hemoglobin concentration
platelet count
white blood cell (leukocyte) count
differential blood cell count
blood cell morphology

Coagulation

prothrombin time
fibrinogen
activated partial thromboplastin time

Serum Chemistry

glucose
urea nitrogen
creatinine
total protein
albumin
globulin
albumin/globulin ratio
alkaline phosphatase
total bilirubin
alanine aminotransferase
gamma glutamyltransferase
aspartate aminotransferase
calcium
inorganic phosphorus
sodium
potassium
chloride

Urinalysis

microscopic examination of sediment
specific gravity

The blood samples were collected from the jugular vein, and the urine samples were collected overnight from sloped pans during the overnight fast, approximately 16 hours.

Anticoagulant was sodium citrate for prothrombin time, activated partial thromboplastin time, and fibrinogen and potassium EDTA for the other hematology tests. Samples for clinical chemistry were collected with no anticoagulant.

Absorption

Absorption was not determined in conjunction with this study. Signs of toxicity served as an indication of absorption.

POSTMORTEM PROCEDURES

Necropsy

After at least 90 days of treatment (on either Day 94 or 97), all animals were weighed, anesthetized with sodium thiopental, exsanguinated, and necropsied. A necropsy was performed on each animal by appropriately trained personnel using procedures approved by board-certified pathologists. Necropsy was conducted under direct supervision of a veterinary pathologist. All findings were recorded. The necropsy included examination of the following:

all orifices
cranial cavity
external surface of the brain; the external surface of the spinal cord and cut surfaces of the brain and spinal cord were examined when tissue trimming was performed.
cervical tissues and organs
thoracic, abdominal, and pelvic cavities and viscera
external surface of the body
nasal cavity and paranasal sinuses

Organ Weights

At the scheduled sacrifice, the following organs (when present) were weighed after careful dissection and trimming of fat and other contiguous tissue:

adrenal (2)
ovary (2)
liver with drained gallbladder
thymus
spleen
kidney (2)
testis with epididymis (2)
thyroid (2) with parathyroid
brain

Organ-to-body weight percentages and organ-to-brain weight ratios were calculated.

Tissue Preservation

The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin:

adrenal (2)
aorta
brain
cecum
colon
duodenum
esophagus
eye (2)
femur with bone marrow (articular surface of the distal end)
gallbladder
heart
ileum
jejunum
kidney (2)
lesions
liver
lung
mammary gland
mandibular lymph node
mesenteric lymph node
ovary (2)
pancreas
pituitary
prostate
rectum
salivary gland [mandibular (2)]
sciatic nerve
skeletal muscle (thigh)
skin
spinal cord (cervical, thoracic, and lumbar)
spleen
stomach
testis with epididymis (2)
thymus
thyroid (2) with parathyroid
trachea
urinary bladder
uterus with cervix and vagina

Histopathology

Tissues (as appropriate) from each animal were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically from Groups 1 and 5[a]. The liver was identified as a possible target organ and was examined from all animals in Groups 2 through 4, as needed, to establish a no-effect level.

Statistical Analyses

Body weights, body weight change, food consumption, total food consumption, clinical pathology (except hemolysis and cellular morphology gradings and routine urinalysis data), fasted terminal body weight, and organ weight data of the treated groups were compared statistically to the data from the same sex of the control group.

Levene's test was done for variance homogeneity. In the case of heterogeneity variance at $p \leq 0.05$, transformations were used to stabilize the variance. Comparison tests take variance heterogeneity into consideration.

One-way analysis of variance (ANOVA) was used (if applicable) to analyze body weights and body weight changes, food consumption, continuous clinical pathology values, and organ weight data. If the ANOVA is significant, Dunnett's t-test was used for control versus treated group comparisons.

Group comparisons to control values were evaluated at the 5.0% two-tailed probability level. Only data collected on or after the first day of treatment were analyzed statistically unless otherwise deemed appropriate.

Rank-transformed data are indicated by footnote on the appropriate tables of this report.

Statistical significance is designated throughout the text of this report by the term *significant*.

---

[a]See Appendix of Protocol Deviations

Specimen, Raw Data, and Final Report Storage

All paper raw data, documentation, records, protocol, specimens, and the final report generated as a result of this study will be archived in the storage facilities of Covance-Vienna for a period of 1 year following submission of the final report to the Sponsor. One year after submission of the final report, all of the aforementioned materials will be sent to the Sponsor. The Sponsor may elect to have the materials retained in the Covance Archives for an additional period of time. All raw data stored on magnetic media will be retained by Covance.

RESULTS

In-life Observations

Mortality and Clinical Observations. A summary of clinical observations is presented in Table 1; individual observations are presented in Appendix 2.

All animals survived to their scheduled sacrifice.

There were no test article-related clinical observations.

Vomitus (white in color, yellow in color, containing food, foreign material, partial/intact capsules or foamy) was noted in animals in the control and all treated groups with similar frequency of occurrence. An attempt was made to redose intact capsules found after dosing; however, there were two instances when retrieved intact capsules were not redosed (also see Appendix of Protocol Deviations).

Other clinical observations noted during the course of the study are of the type commonly seen in laboratory animals of this age, sex, and strain and are not considered treatment related.

Body Weights. Mean body weight data are presented in Table 2; body weight change data are presented in Table 3. Individual body weight data are presented in Appendix 3.

All animals gained weight during the course of the study. There were no significant or biologically relevant differences in mean body weight or body weight change data between control and treated animals.

Food Consumption. Mean and total food consumption data are presented in Table 4. Individual food consumption data are presented in Appendix 4.

There were no treatment-related changes in food consumption. The significant elevations noted in the food consumption means are not considered test material related due to the fact that they occurred infrequently, without respect to dose, and were generally small.

Ophthalmic Findings. Ophthalmic findings are discussed in the Ophthalmology Report.

The finding of retinal folds in female G35573 was noted at the preinitiation examination and is not related to compound effects.

Clinical Pathology

Mean values are presented in Tables 5 (hematology) and 6 (serum chemistries), and individual values are presented in Appendix 5 (hematology, serum chemistries, and urinalysis). Findings are further discussed in the Clinical Pathology Report.

The significant differences in the hematology and coagulation data are not attributed to treatment due to the low magnitude of the changes, the lack of dose dependence, and/or the occurrence of the change during pretreatment. With the exception of alanine aminotransferase, the significant differences in the clinical chemistry are also considered incidental to treatment with the test material.

Elevations in alanine aminotransferase values at Week 13 for individual animals in Group 5 correlated with the severity of histologic findings, (described below) in the livers of these dogs.

Anatomical Pathology

Gross pathology findings are summarized in Table 7 and presented individually in Appendix 6.

None of the macroscopic observations are considered test material related.

Organ weight data are presented in Table 8. Individual data are presented in Appendix 6.

There was no evidence of compound-related organ weight changes in the treated groups.

Microscopic findings are summarized in Tables 9 and 10 and presented individually in Appendix 6. The findings are further discussed in the Pathology Report.

Compound-related histopathologic changes were present in the livers of nearly all Group 5 males and females.

Specific findings included hepatocellular degeneration/necrosis and an increased severity of hepatic inflammation. Hepatocellular degeneration/necrosis was multifocal in distribution, graded minimal (+1) to moderate (+3) in severity, and correlated to the elevations in alanine aminotransferase values present in several Group 5 dogs. An increased severity (slight to moderate) of hepatic inflammation was associated with these foci of degeneration/necrosis and was characterized by multifocal infiltrates of macrophages within the hepatic parenchyma. In animals G35578 (Group 5 male) and G35580 (Group 5 female), a low magnitude (minimal to slight) of periportal fibrosis was also present.

There was no microscopic evidence of compound-related hepatocellular degeneration/ necrosis or increased hepatic inflammation in the animals from Groups 2-4. Although inflammation was slightly increased in the liver of animal G35555 (Group 2 female), there was no evidence of a clinical chemistry correlation for that animal and, more importantly, there was no microscopic evidence of increased hepatic inflammation in any of the remaining Group 2 dogs or in the Group 3 and 4 dogs. Therefore, the increased hepatic inflammation in Group 2 animal G35555 is considered to be an isolated change that is unrelated to the test material. Additionally, a low magnitude of hepatic inflammation was present in the livers of all of the control dogs, indicating that this is a common spontaneous finding.

DISCUSSION AND CONCLUSION

The purpose of the study was to evaluate the toxicity of TKA 40082 when administered daily by capsule to dogs for at least 90 days.

When TKA 40082 was given to beagle dogs by capsule twice daily at doses of 10, 50, 200, and 1000 mg/kg/day, divided evenly over two daily doses, there were no effects noted in the clinical observations, body weight, food consumption, or ophthalmologic examinations. At necropsy, observations were typical of beagle dogs of this age. Microscopic changes consisting of hepatocellular degeneration and necrosis and increased severity of hepatic inflammation were present in the livers of dogs which received 1000 mg/kg/day. These liver findings correlated with elevations in alanine aminotransferase in these dogs. There were no additional test material-related changes noted in the clinical pathology data or microscopic observations. Based upon the histological findings and elevated alanine aminotransferase levels at 1000 mg/kg/day, the no-observable-effect level (NOEL) for TKA 40082 is 200 mg/kg/day when divided evenly over two daily capsule doses for at least 90 days.

E Roxanne May for — April 30, 1999

Jenny L. Craver, AAS, LVT
Study Coordinator

Date

Marie E. McKeon — April 30, 1999

Marie E. McKeon, MPhil, DABT
Study Director

Date

OPHTHALMOLOGY REPORT

Method

Ophthalmoscopic evaluations were performed once prior to initiation of dosing and on Day 91. The pupils were dilated with 1% Mydriacyl® and examined using indirect ophthalmoscopy, as required by protocol.

Results

Examinations of the dogs assigned to study revealed the following ophthalmoscopic finding:

Ophthalmoscopic Finding

Animal Number	Group	Sex	Day	Finding
G35573	4	F	91	Fundus, retinal fold(s), unilateral left-multifocal.

Key: F = Female

The finding of retinal folds in female G35573 was noted at the preinitiation examination and is not related to compound effects.

Conclusion

The observation noted at Day 91 is not attributed to test material administration.

Robert L. Ridgway, DVM, Diplomate, ACLAM

29 Apr 99
Date

CLINICAL PATHOLOGY REPORT

Summary

The test material, TKA 40082, was administered in oral capsules at dosage levels of 0 (empty capsule control), 10, 50, 200, and 1000 mg/kg/day (Groups 1-5, respectively) to beagle dogs for at least 90 days. Hematology, coagulation, serum chemistry, and urinalysis tests were performed on samples collected at Weeks -1, 8, and 13. The elevations in alanine aminotransferase (ALT) activity observed in several Group 5 animals at Week 13 are attributed to the administration of TKA 40082 and correlate with the hepatocellular degeneration/necrosis noted histologically in these animals at terminal sacrifice.

Results and Discussion

Hematology and Coagulation. The significant differences observed in the hematology and coagulation data and differential leukocyte counts cannot be attributed to the administration of TKA 40082 due to the low magnitude of the changes, the lack of dose dependence, and/or the presence of the difference prior to treatment (Week -1); they will not be characterized further. The cellular morphology results were generally unremarkable and comparable between the groups at Weeks -1, 8, and 13. The cause for the low platelet count in Group 2 male G35551 at Weeks -1 and 8 is not apparent from the data examined (clinical observations, body weights, body weight changes, food consumption, necropsy findings, organ weights, and remaining clinical pathology data). Although the value increased at Week 13, it remained below 200,000 platelets/µL. No other clinical pathology abnormalities were observed for this male at any interval.

Serum Biochemistry. The significant changes seen in the clinical chemistry data are considered incidental to treatment with the test material due to the low magnitude of the differences, the lack of dose dependence, and/or the occurrence of the change prior to treatment (Week -1); they will not be itemized. The increases in ALT values seen in several Group 5 animals (males G35575 and G35576 and female G35579) at Week 13 are consistent with the treatment-related hepatocellular degeneration and necrosis (with inflammatory component) observed histologically in these animals at terminal sacrifice.

Urinalysis. The urine specific gravity readings and the microscopic sediment examination results were generally unremarkable and similar among the groups at Weeks -1, 8, and 13, with one exception. Trace amounts of fine or coarse granular casts were noted in the urine of Group 3 male G35560 at Weeks 8 and 13 and in Group 4 male G35577 at Week 13. The casts are not considered to be related to treatment due to the low number of animals affected and the lack of dose dependence.

Conclusion

The elevations in ALT activity observed in several Group 5 animals at Week 13 are attributed to the administration of TKA 40082 and correlate with the hepatocellular degeneration/necrosis noted histologically in these animals at terminal sacrifice.

Renée C. Pearson

Renée C. Pearson, MS, DVM, Diplomate, ACVP
Clinical Pathologist

April 29, 1999
Date

PATHOLOGY REPORT

Forty beagle dogs received the oral (capsule) administration of TKA 40082 at doses of 0, 10, 50, 200, and 1000 mg/kg/day (Groups 1-5, respectively) for at least 90 days.

Treatment-related histopathologic changes consisting of hepatocellular degeneration and necrosis and an increased severity of hepatic inflammation were present in the livers of the Group 5 males and females. These liver findings correlate to the elevations in alanine aminotransferase present in several animals from Group 5.

METHODS

Forty young adult beagle dogs were randomly placed into treatment groups as follows:

Group No.	No. of Animals		Dose Levels
	Male	Female	mg/kg/day
1 (Control)	4	4	0
2 (Low)	4	4	10
3 (Mid)	4	4	50
4 (Mid-High)	4	4	200
5 (High)	4	4	1000

The treated dogs (Groups 2-5) received the test material, TKA 40082. Following at least 90 days of compound administration, all dogs were sacrificed and tissues were examined microscopically according to protocol. Specifically, complete tissues from Groups 1 and 5 and livers (target tissue) from Groups 2-4 were examined.

RESULTS AND DISCUSSION

Mortality

All animals survived until the scheduled sacrifice.

Clinical Pathology

Clinical pathology findings are detailed in the clinical pathology report. The elevations in alanine aminotransferase values noted in several Group 5 dogs correlate to the hepatocellular degeneration/necrosis noted microscopically in these animals and are considered to be a compound-related finding.

Anatomical Pathology

Body and Organ Weights. Terminal body and organ weight findings are detailed in the main report. Mean terminal body weights were comparable between control and treated groups. There was no evidence of compound-related organ weight changes in the treated groups.

Macroscopic Observations. Gross pathology findings are detailed in the study report. None of the macroscopic observations are considered drug related. Gross observations were present in the reproductive tracts of females from all groups that represent normal cycling (estrous) activity and occurred unrelated to treatment.

Microscopic Observations. Compound-related histopathologic changes were present in the livers of nearly all Group 5 males and females. Specific findings included hepatocellular degeneration/necrosis and an increased severity of hepatic inflammation. Hepatocellular degeneration/necrosis was multifocal in distribution, graded minimal (+1) to moderate (+3) in severity, and correlated to the elevations in alanine aminotransferase values present in several Group 5 dogs. An increased severity (slight to moderate) of hepatic inflammation was associated with these foci of degeneration/necrosis and was characterized by multifocal infiltrates of macrophages within the hepatic parenchyma. In animals G35578 (Group 5 male) and G35580 (Group 5 female), a low magnitude (minimal to slight) of periportal fibrosis was also present.

There was no microscopic evidence of compound-related hepatocellular degeneration/ necrosis or increased hepatic inflammation in the animals from Groups 2-4. Although inflammation was slightly increased in the liver of animal G35555 (Group 2 female), there was no evidence of a clinical chemistry correlation for that animal and, more importantly, there was no microscopic evidence of increased hepatic inflammation in any of the remaining Group 2 dogs or in the Group 3 and 4 dogs.

Therefore, the increased hepatic inflammation in Group 2 animal G35555 is considered to be an isolated change that is unrelated to the test material. Additionally, a low magnitude of hepatic inflammation was present in the livers of all of the control dogs, indicating that this is a common spontaneous finding.

A variety of microscopic findings were present with similar incidence in dogs from all groups and are considered to be typical, incidental, or spontaneous changes commonly seen in this age of beagle dog and occurred without relation to treatment. The enlarged ovaries and thickened uterus, cervix, vagina, and mammary present in several control and/or treated dogs represented normal cyclic (estrous) activity and were therefore considered unremarkable microscopically.

Ricardo V. Quander, DVM, Diplomate, ACVP
Pathologist

4/30/99
Date

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COMMENTS ON THE DATA

Various models of calculators, computers, and computer programs were used to analyze data in this study. Because different models round off or truncate numbers differently, values in some tables (e.g., means, standard deviations, or individual values) may differ slightly from those in other tables, from individually calculated data, or from statistical analysis data. Neither the integrity nor the interpretation of the data was affected by these differences.

The number of animals listed in the heading of the summary tables for clinical observations reflects the number of animals assigned to each group at the start of the study.

The summary tables for clinical observations indicates the number of animals for which a condition was observed without regard to the specific nature, severity, reversibility, number of incidences/animal, or the length of time the condition persisted.

Only observations for each animal other than normal, with the exception of qualitative food consumption, are indicated on the summary and individual clinical observations tables.

Each animal with observations recorded as "Normal" throughout the study has the comment "Animal has no significant findings" indicated on the individual clinical observations tables.

The specific details for comments in the individual clinical observations tables that are indicated with a "C" can be found at the end of each group for each sex.

Only animals with observations recorded are included in the individual clinical observations tables.

Only animals with observations other than no visible lesions are indicated on the individual ophthalmic observation tables.

The day of initiation of treatment is "Day 1, Week 1." Body weight data are entered at the start of a study week (e.g., a body weight recorded on Day 1 is considered a Week 1 body weight, a body weight recorded on Day 8 is considered a Week 2 body weight). Body weight gain data are calculated from the first day of the study to the first day of the following study week (e.g., Week 1 values are calculated from Day 1 through 7) and are indicated in the tables with the day being the first day of the following week (e.g., Week 1 values are indicated as "Day 8.") Weekly food consumption is calculated from the first day of the study week to the first day of the following study week (e.g., Week 1 values are

calculated from Days 1 through 7.) but are indicated in the tables with the day at the start of the week (e.g., Week 1 values are indicated as "Day 1".

Food consumption values are reported in whole numbers; however, HPTS carries food consumption values to one place to the right of the decimal for food efficiency and test material consumption calculations. The differences in values generated do not influence the interpretation of the calculation.

HPTS will not include an animal on the individual food consumption data tables if that animal does not have at least one valid food consumption data value for the interval covered in the table.

The comment "SPILLED" on individual food consumption data tables indicates that food consumption was not recorded due to spillage or contamination during the interval.

The comment "EXCLUDE" on individual food consumption data tables indicates that the food consumption value was not considered realistic and was excluded at the request of the Study Director.

The comment "CNTMTD" on individual food consumption data tables indicates that food consumption was not recorded due to contamination of the diet with urine or feces in the food container.

The comment "NOT TAKEN" on individual food consumption data tables indicates the animal died before the end of the food consumption interval.

The comment "TECH SPILL" on individual food consumption data tables indicates that food consumption was not recorded due to food spillage caused by technician error.

Differences in the population size (N) on the summary tables for clinical and anatomical pathology are explained on the individual data tables or in the Protocol Deviations section.

The calculation for Daily Body Weight Gain =

$$\frac{\text{Last Body Weight of Interval} - \text{First Body Weight of Interval}}{\text{Day of Last Body Weight of Interval} - \text{Day of First Body Weight of Interval}}$$

and: Day Factor =

$$(\text{Food Consumption Start Day} - \text{Day of First Body Weight of Interval}) + \frac{\text{Food Consumption Interval}}{2}$$

and: Food Consumption Interval =
Food Consumption End Day - Food Consumption Start Day

The calculation for relative food consumption is:

$$\text{Relative Food Consumption (g/kg/day)} = \frac{\text{Food Consumption (g) for Interval (week)}}{\text{Body Weight (kg)} \times 7 \text{ days/week}}$$

During microscopic examination of blood smears, the following items were noted:

At Week -1, large platelets (few) were noted for G35551, G35574, G35555, G35563.

The Week 8 urine sample for G35560 was collected 2 days later than other samples.

CODES, ABBREVIATIONS, AND UNITS

General Codes and Abbreviations
Codes for Clinical Pathology
Abbreviations and Units for Clinical Hematology
Abbreviations and Units for Clinical Chemistry
Abbreviations and Units for Clinical Urinalysis
Codes for Anatomical Pathology

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

General Codes and Abbreviations

WK	Week
N	Number of measurements in a group
Mean; MEAN	Arithmetic mean
CAM	Covariate-adjusted mean
SD; S.D.; STAND DEV; STANDARD DEV; sd STD. DEV	Standard deviation
#; N; No.	Number
CV	Coefficient of variation
DLAM	Department of Laboratory Animal Medicine
GLP	Good Laboratory Practice Regulations
SOP	Standard operating procedures
NVL	No visible lesions
P	Present
C	Comment found at the end of each group for each sex
UNSCHED or SCHED	Unscheduled or scheduled
DISPATCH	Observations transferred from the in-life module of the data collection system to the necropsy module for reference during necropsy. Observations are duplicates of the last in-life observations.
TBW	Terminal body weight
BT	Body temperature
HR	Heart rate
RR	Respiration rate
CO	Clinical observation
M or ♂	Males
F or ♀	Females
CSO	Cageside observations
PDO	Postdose observations

Units of Measure

G	Gram
KG	Kilogram
MG	Milligram
PG	Picogram
L	Liter
DL	Deciliter
FL	Femtoliter
ML, mL	Milliliter

General Codes and Abbreviations (Continued)

Units of Measure

MI/UL	Millions/microliter
TH/UL	Thousands/microliter
MEQ	Milliequivalents
EU	Ehrlich units
PPM	Parts per million

Statistical Annotations

RT	Rank transformation
RTB	Rank transformation, both sexes
RTF	Rank transformation, females only
RTM	Rank transformation, males only
*	Significantly different from control value, $p \leq 0.05$
**	Significantly different from control value, $p \leq 0.01$

Codes for Clinical Pathology

GENERAL CODES

QS/QNS	Quantity not sufficient
NR/QNR	No repeat (sample volume not sufficient for repeat analysis)
PLASMO	Plasmodium
NO AGG	No aggregation
UTD	Unable to determine
NO COAG	No coagulation
NOCG	Hypocoagulability; no clot
CGERR	Hypercoagulability; clots too fast
EDTA	Ethylene diamine tetra acetate (anticoagulant)
S	Seconds
PER HPF	Microscopic findings per high power field
PER LPF	Microscopic findings per low power field
NT	No test performed
NSR	No sample received
BDL	Below detectable limit
CLOT	Clotted sample
SUFA	Sample unsuitable for analysis
U	Units
UMOL	Micromoles
MMOL	Millimoles
MOS	Milliosmoles
ML/MN/KG	Milliliters/minute/kilogram
ND	None detected
TNTC	Too numerous to count

Codes for Clinical Pathology (Continued)

RESULTS NOT INCLUDED IN STATISTICAL ANALYSES

Intervals with or specific groups with numbers of animals less than 3.
Nucleated red blood cell means.
Samples from animals at unscheduled intervals
Prothrombin times greater than 50 seconds
Activated partial thromboplastin times greater than 110 seconds

HEMOLYSIS AND BLOOD CELL MORPHOLOGY

The following scales were used for hemolysis in serum and plasma and for blood cell morphology:

Hemolysis		Cell Morphology			
0	Not present	-	None present	-	None present
1	Trace	T	Trace numbers present	F	Few cells present
2	Slight	1	Slight numbers present	M	Many cells present
3	Moderate	2	Moderate numbers present		
4	Marked	3	Marked numbers present		
5	Severe	4	Severe numbers present		

URINE APPEARANCE

Color Abbreviation				Clarity	
Straw	S	Green	G	Clear	CL
Yellow	Y	Brown	BR	Slightly cloudy	SC
Dark yellow	D	Blue	BL	Cloudy	CY
Amber	A	Colorless	CO	Turbid	T
Red/red-brown	R	Other	O		
Orange	OR				

Codes for Clinical Pathology (Continued)

URINE AND FECAL ANALYSIS

Multistix® Strip

Urine Glucose		Urine Ketones		Urine Blood	
-	Negative	-	Negative	-	Negative
T	100 mg/dL	T	5 mg/dL	T	Trace
1	250 mg/dL	1	15 mg/dL	1	Small
2	500 mg/dL	2	40 mg/dL	2	Moderate
3	≥1,000 mg/dL	3	≥80 mg/dL	3	Large

Urine Nitrite		Urine Protein		Urine Bilirubin	
-	Negative	-	Negative	-	Negative
+	Positive	T	Trace	1	Small
		1	30 mg/dL	2	Moderate
		2	100 mg/dL	3	Large
		3	≥300 mg/dL		

Clinitek® 200+ Analyzer

Urine Glucose		Urine Ketones		Urine Blood	
NEG	Negative	NEG	Negative	NEG	Negative
TR	100 mg/dL	TR	5 mg/dL	TR	Trace
1	250 mg/dL	1	15 mg/dL	1	Small
2	500 mg/dL	2	40 mg/dL	2	Moderate
3	≥1,000 mg/dL	3	≥80 mg/dL	3	Large

Urine Nitrite		Urine Protein		Urine Bilirubin	
NEG	Negative	NEG	Negative	NEG	Negative
POS	Positive	TR	Trace	1	Small
		1	30 mg/dL	2	Moderate
		2	100 mg/dL	3	Large
		3	≥300 mg/dL		

Ictotest® Urine Bilirubin		Clinitest® Urine Reducing Substances		Hemoccult® Fecal Occult Blood	
-	Negative	-	Negative	-	Negative
+	Positive	T	5 mg/dL	+	Positive
		1	15 mg/dL		
		2	40 mg/dL		
		3	≥80 mg/dL		

Codes for Clinical Pathology (Continued)

MICROSCOPIC EXAMINATION OF URINE

Gradings			
Casts, red and white blood cells, and epithelial cells		Amorphous, crystals, bacteria, yeast, sperm, and mucus	
-	none seen	-	none seen
T	1-4	T	occasional
1	5-10	1	few
2	11-25	2	moderate
3	26-50	3	many
4	>50		

Abbreviations for Clinical Hematology

Test	Abbreviation
Hematocrit	HCT
Hemoglobin	HGB
Red Blood Cell	RBC
White Blood Cell	WBC
Mean Platelet Value	MPV
Red Cell Distribution	RDW
Hemoglobin Distribution	HDW
Platelet Distribution	PDW
Platelet Crit	PCT
Platelet Count	PLATELET
Mean Corpuscular Volume	MCV
Mean Corpuscular Hemoglobin	MCH
Mean Corpuscular Hemoglobin Concen	MCHC
Reticulocyte Count	RETIC
Absolute Retic	A RETIC
Nucleated RBC's	NRBC
Corrected Leukocyte Count	COR WBC
Blast Cells	BLAST
Promyelocyte/Myelocyte Cells	PRO/MYEL
Metamyelocytes	META
Band Neutrophils	BAND
Segmented Neutrophils	SEG
Lymphocytes	LYMPH
Monocytes	MONO
Eosinophils	EOSIN
Basophils	BASO
Coagulation Hemolysis	COAGHEM
Prothrombin Time	PT
Activated Partial Throm Time	APTT
Fibrinogen	FIBRIN
Thrombin Time	TT
Platelet Aggregation - Inhib	PAGG/INH
Platelet Aggregation - ADP	PAGG/ADP
Fibrin Degradation Products - D-Dimer	FDP
Myeloid/Erythro Ratio	M/E Ratio
Myeloid	MYELOID
Erythro	ERYTHRO
Micro Hematocrit (Spun)	HCT SPUN

Abbreviations for Clinical Hematology (Continued)

Test	Abbreviation
Erythrocyte Sedimentation Rate	ESR
Heinz Bodies	HEINZ
Platelet Estimate	PLT EST
Anisocytes	ANISO
Echinocytes	ECHINO
Target Cells	TARGET CELLS
Hypochromic Cells	HYPO
Microcytes	MICRO
Poikilocytes	POIK
Acanthocytes	ACANTH
Basophilic Stip Cells	BASOSTIP
Polychromatophilic Cells	POLY
Howell-Jolly Bodies	HJBODY
Dohle Bodies	DOHLE
Reactive Lymphocytes	REACTLYM
Plasmodium	PLASMO
Schistocytes	SCHISTO
Toxic Granulation	TOXIC
Rectangular red blood cells	RECRBC
Folded red blood cells	FLDRBC
Smudge cells	SMUDGE
Plasmodium	PLASMO
Platelet clumps	PLTCLP
Spherocytes	SPHERO
Macrocytes	MACRO
Stomatocytes	STOMAT
Microcytes	MICRO
Rouleaux	ROULEX
Elliptocytes	ELLIP
Acanthocytes	ACANTH

Abbreviations for Clinical Chemistry

Test	Abbreviation
Plasma Hemolysis	PLHEM
Serum Hemolysis	SERUMHEM
Total Protein	T PROT
Albumin	ALBUMIN
Globulin	GLOBULIN
Albumin/Globulin Ratio	A/G RATIO
Alkaline Phosphatase	ALK P
Total Bilirubin	T BILI
Direct Bilirubin	D BILI
Indirect Bilirubin	I BILI
Urea Nitrogen	UREA N
Creatinine	CREAT
Blood Urea Nitrogen/Creatinine Ratio	BUN/CRE
Glucose	GLUCOSE
Aspartate Aminotransferase	AST
Alanine Aminotransferase	ALT
Creatine Kinase	CK
Dehydrogenase	LDH
Gamma-Glutamyltransferase	GGT
Uric Acid	UAC
Calcium	CALCIUM
Inorganic Phosphorus	IN PHOS
Amylase	AMYLASE
Magnesium	MAGNES
Anion Gap	ANION GAP or AN GAP
Total Cholesterol	T CHOL
Triglycerides	TRIGLY
Sodium	SODIUM
Potassium	POTAS
Chloride	CHLORIDE
Sodium/Potassium Ratio	NA/K
High-Density Lipoprotein	HDL
Ldl Lipoprotein	LDL
Ldl Lipoprotein Cholesterol	LDL
Albumin (Rabbits)	ALBUMIN
High Density Lipoprotein	HDCHOL or HDLCHOL
Low Density Lipoprotein	LDCHOL or LDLCHOL
Very Low Density Lipoprotein	VLDCHOL or VLDLCHOL
Serum Electrophor - Albumin	SELA-ALB

Abbreviations for Clinical Chemistry (Continued)

Test	Abbreviation
Serum Electrophor - Alpha-1	SELA-A1
Serum Electrophor - Alpha -2	SELA-A2
Serum Electrophor - Beta	SELA-B
Serum Electrophor - Gamma	SELA-G
CSF Electrophoresis - Albumin	CSF ALB
CSF Electrophoresis - Alpha 1	CSF A1
CSF Electrophoresis - Alpha 2	CSF A2
CSF Electrophoresis - Beta	CSF B
CSF Electrophoresis - Gamma	CSF G
Ck Isoenzymes (CK1) (BB) Fraction	CK1 (BB)
Ck Isoenzymes (CK2) (MB) Fraction	CK2 (MB)
Isoenzymes (CK3) (MM) Fraction	CK3 (MM)
Plasma Cholinesterase - Butyrl Thio	PCHE-BT
Brain Cholinesterase	BCHE
Plasma Cholinesterase	PLCHE
Erythrocyte Cholinesterase	RBCCHE
Serum Cholinesterase	CHOLINES
Whole Blood Cholinesterase	WBCHE
Serum Iron	IRON
Total Serum Iron Binding Capacity	TIBC
Percent Saturation	% SATUR or % SATURATION
Unsaturated Iron Binding Capacity	UIBC
Leucine Amino Peptidase	LAP
Phospholipid	P LIPID
Sorbitol Dehydrogenase	SDH
Total Bile Acids	TBILE AC
Total Carbon Dioxide	T CO2
Lipase	LPASE
Aldolase	ALDOLASE
Acid Phosphatase	ACID P
Cerebrospinal Fluid - Total Protein	CSF TP
Body Fluid - Protein	BF-TPROT
Body Fluid - Specific Gravity	BF-SPGR
Free Fatty Acids	FFA
5'Nucleotidase	5'NUCLEO
Lithium	LITHIUM
Ionized Calcium	ION CA
Ionized Calcium pH	ION PH
Creatinine Plus	CREAT +
Serum Osmolality	S OSMOL

Abbreviations for Clinical Urinalysis

Test	Abbreviation
Hydrogen Ion Concentration	PH
Specific Gravity	SP GR
Glucose	GLUCOSE
Ketones Bodies	KETONES
Protein	PROTEIN
Bilirubin	BILI or BILIRUB
Occult Blood-Urine	OC BLD-U
Urobilogen	UROBIL
Occult Blood-Feces	OC BLD-F
Urine Volume	U VOL or URINEVOL
Urine Transparency	UTRANS
Urine Color	UCOLOR
Ova and Parasites	O&P
Urine Nitrate	NITRATE
Red Blood Cells	RBC
White Blood Cells	WBC
Epithelial Cells	EPITH
Amorphous Crystals	AMORPH
Crystals	CRYSTALS
Bilirubin	B
Leucine	L
Tyrosine	T
Cholesterol	CH
Hippuric acid	H
Cystine	CY
Ammonium biurate	AB
Calcium oxalate monohydrate	CO
Bacteria	BACTERIA
Casts	CASTS
Hyaline	H
Fine granular	FG
Coarse granular	CG
Epithelial cell	E
Waxy	W
Fatty	F
Red cell	R
Leukocyte	L
Yeast	YEAST
Sperm	SPERM
Mucus	MUCUS

Codes for Anatomical Pathology

Code	Definition
	ANIMAL DEATH CODES
1-6	Interim sacrifices 1 through 6
T	Terminal sacrifice
U	Postrecovery sacrifice 1
V	Postrecovery sacrifice 2
A	Accidental Death
B	Gavage accidental death
D	Found dead
M	Moribund sacrifice
P	Preexperimental death
R	Removed from study
O	Other type of unscheduled death
UNSCHED	Unscheduled death
SCHED	Scheduled death
	ORGAN WEIGHING STATUSES
NOT TAKEN	Organ weight not taken; no explanation given
MISSING	Organ missing or lost
UNSUITABLE	Organ technically unsuitable for weighing
AUTOLYTIC	Organ autolytic and could not be weighed
EXCLUDE	Weight has been taken, but will be excluded from all calculations
	OTHER SYMBOLS AND NOTATIONS
H-	Finding noted during processing of tissues in histology (precedes keyword).
	SYMBOLS PREFACING NEOPLASTIC FINDINGS
B-	Primary, benign neoplasm
M-	Primary, malignant neoplasm
N-	Metastatic neoplasm
I-	Locally invasive neoplasm
X-	Other neoplasm

Codes for Anatomical Pathology (Continued)

Code	Definition
Locations of Tissue Masses Observed Grossly	
DFL	Dorsal-Front-Left
DFR	Dorsal-Front-Right
DHL	Dorsal-Hind-Left
DHR	Dorsal-Hind-Right
DFM	Dorsal-Front-Mid
DHM	Dorsal-Hind-Mid
VFL	Ventral-Front-Left
VFR	Ventral-Front-Right
VHL	Ventral-Hind-Left
VHR	Ventral-Hind-Right
VFM	Ventral-Front-Mid
VHM	Ventral-Hind-Mid
Distribution of Findings	
Focal	
Diffuse	
Multifocal	
Grades for Severity or Amount	
1	Minimal - the least amount of change that can be observed with the light microscope
2	Slight - less than average amount of change, but readily discernible as abnormal
3	Moderate - the average amount of change that is expected for a lesion
4	Moderately severe (marked) - a marked amount of change with possible loss of function of the affected cells or organs
5	Severe - a great amount of change with probable loss of function of the affected cell or organs and frequently involves large areas of the organ
Other Microscopic Codes	
TL	Total
P	Finding present
-	Finding not present
MN	Mean

Codes for Anatomical Pathology (Continued)

Organ/Tissue/Site Abbreviations[a]	Definition
LN	Lymph node
GALLBLADD	Gallbladder
GL	Gland or Glandular
NONGL	Nonglandular
SALIV GL	Salivary gland
MAND or MANDIB	Mandibular
MESEN or MES	Mesenteric
ANTERIOR	Anterior
ABDOM	Abdominal
TRACHEOBRON	Tracheobronchial
CATHETER EXIT	Catheterization site: exit site from the body
CATHETER ENTRANC	Catheterization site: entrance site into the vessel
CATHETER EXIT	Catheterization site: tissues (vascular or extravascular) associated with the catheter near its tip
EPIDID	Epididymis or Epididymides
PARATHYR	Parathyroid

[a] Tissue abbreviations are too numerous to list all possibilities.

TABLE 1
SUMMARY OF CLINICAL OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

DAYS 1-97

NUMBER OF ANIMALS AFFECTED

CATEGORY / KEYWORD / QUALIFIER	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
DOSE: MG/KG/DAY	0	10	50	200	1000	0	10	50	200	1000
NUMBER:	4	4	4	4	4	4	4	4	4	4
*** TOP OF LIST ***										
APPEARANCE										
THIN	1	0	1	1	1	0	1	0	0	1
DISCHARGE										
VOMITUS										
WHITE IN COLOR	1	0	0	0	1	0	0	1	0	1
YELLOW IN COLOR	0	0	0	1	0	0	1	0	0	0
CONTAINING FOOD	3	0	0	1	2	3	2	2	0	2
FOAMY	2	2	1	0	2	4	1	1	0	2
FOREIGN MATERIAL	0	0	0	1	0	0	0	0	0	0
INTACT CAPSULE	4	2	2	0	3	1	1	2	1	3
PARTIAL CAPSULE	0	0	1	0	2	3	1	1	0	1
EXCESSIVE SALIVATION	0	0	0	1	0	0	0	0	0	0
APPEARS TO BE CYCLING	0	0	0	0	0	2	3	2	2	2
EXCRETION										
DISCOLORED FECES										
RED IN COLOR	1	0	0	0	0	1	1	0	0	0
WHITE IN COLOR	0	0	0	0	1	0	0	0	0	2
YELLOW IN COLOR	1	0	0	0	1	0	0	0	0	1
LIQUID FECES	2	0	0	0	0	1	1	1	0	1
MUCOID FECES	1	0	0	2	0	1	2	0	0	1
NO FECES	0	1	1	0	1	0	0	0	0	0
NON-FORMED FECES	4	3	3	4	1	3	4	3	3	2
THICK URINE	0	0	1	0	0	0	0	0	0	0
OTHER	0	0	0	1	0	0	0	0	0	0
EYES										
CLEAR DISCHARGE										
EYE-LEFT	0	1	0	0	0	1	0	0	1	1
EYE-RIGHT	0	1	0	0	0	1	0	0	1	0
EYES	0	0	0	0	0	0	0	0	0	1

TABLE 1
SUMMARY OF CLINICAL OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

DAYS 1-97

NUMBER OF ANIMALS AFFECTED

CATEGORY / KEYWORD / QUALIFIER	MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5
SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
DOSE: MG/KG/DAY	0	10	50	200	1000	0	10	50	200	1000
NUMBER:	4	4	4	4	4	4	4	4	4	4
EYES										
INJECTED SCLERA										
EYE-LEFT	1	4	2	1	3	2	1	1	1	1
EYE-RIGHT	1	1	2	0	1	2	0	0	1	0
EYES	1	4	1	1	1	3	1	2	2	1
SKIN & PELAGE										
ALOPECIA										
LIMB-HIND-LEFT	0	0	0	0	0	0	0	0	1	0
LIMB-HIND-RIGHT	0	0	0	0	0	0	0	0	1	0
MUZZLE	0	1	0	0	0	0	0	0	0	0
BROKEN SKIN										
MUZZLE	0	1	0	0	0	0	0	0	0	0
RED SKIN										
MUZZLE	0	1	0	0	0	0	0	0	0	0
EARS	0	1	1	0	0	0	0	0	0	0
SCAB(S)										
FOOT-LEFT	0	1	0	0	0	0	0	0	0	0
INGUINAL-LEFT	0	0	0	0	0	0	1	0	0	0
INGUINAL-RIGHT	0	0	0	0	0	0	1	0	0	0
NOSE	0	0	0	0	0	0	0	1	0	0
FUNDUS										
RETINAL FOLD(S)										
UNILATERAL LEFT-MULTIFOCAL	0	0	0	0	0	0	0	0	1	0
EYE EXAM										
NO VISIBLE LESIONS	4	4	4	4	4	4	4	4	3	4

*** END OF LIST ***

TABLE 2
SUMMARY OF BODY WEIGHT DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
1	N	4	4	4	4	4	4	4	4	4	4
RTF	MEAN	9.0	8.5	9.1	9.3	9.0	7.9	9.1	8.7	8.6	8.2
	S.D.	0.60	0.56	0.48	0.64	1.09	0.34	0.79	0.61	1.11	0.60
8	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.2	8.7	9.1	9.4	8.9	8.0	9.1	8.8	8.7	8.2
	S.D.	0.93	0.59	0.46	0.69	1.06	0.52	0.65	0.67	0.99	0.68
15	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.6	8.9	9.3	9.4	9.3	8.1	9.2	8.9	8.9	8.2
	S.D.	1.06	0.54	0.47	0.59	1.26	0.57	0.98	0.70	0.98	0.72
22	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.6	8.8	9.2	9.6	9.3	8.3	9.4	9.0	9.1	8.3
	S.D.	0.85	0.32	0.67	0.61	1.32	0.61	1.16	0.67	1.07	0.72
29	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.7	9.0	9.3	9.9	9.3	8.4	9.4	9.2	9.2	8.5
	S.D.	1.01	0.41	0.81	0.57	1.28	0.53	0.95	0.70	1.09	0.73
36	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.7	9.1	9.3	9.7	9.4	8.5	9.7	9.2	9.2	8.5
	S.D.	1.03	0.43	0.83	0.64	1.20	0.51	0.90	0.70	0.88	0.66
43	N	4	4	4	4	4	4	4	4	4	4
	MEAN	9.8	9.1	9.3	10.0	9.4	8.5	9.9	9.3	9.2	8.6
	S.D.	1.19	0.51	0.78	0.71	1.41	0.30	0.88	0.85	1.06	0.74
50	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.0	9.1	9.3	9.8	9.3	8.7	9.8	9.3	9.2	8.4
	S.D.	1.06	0.47	0.88	0.62	1.53	0.47	0.88	0.85	1.06	0.84
57	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.1	9.3	9.5	10.2	9.6	8.7	9.9	9.4	9.4	8.6
	S.D.	1.16	0.53	0.87	0.76	1.43	0.47	0.87	0.83	0.87	0.71

RTF - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES OF FEMALE DATA

TABLE 2
SUMMARY OF BODY WEIGHT DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
64	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.1	9.4	9.4	10.0	9.6	8.7	9.9	9.6	9.4	8.6
	S.D.	0.99	0.70	0.74	0.63	1.37	0.34	0.87	0.99	0.91	0.69
71	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.0	9.6	9.5	10.3	9.6	8.8	9.8	9.7	9.3	8.6
	S.D.	1.20	0.61	0.64	0.72	1.37	0.41	0.80	0.97	0.85	0.59
78	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.2	9.7	9.5	10.4	9.7	9.0	10.1	9.8	9.7	8.7
	S.D.	1.03	0.54	0.84	0.73	1.51	0.50	0.60	0.90	0.92	0.58
85	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.2	9.7	9.6	10.4	9.9	8.9	10.2	9.9	9.7	8.7
	S.D.	1.01	0.76	1.09	0.88	1.61	0.56	0.66	0.95	0.98	0.56
92	N	4	4	4	4	4	4	4	4	4	4
	MEAN	10.2	9.5	9.6	10.5	9.9	9.1	10.3	9.8	9.5	8.8
	S.D.	1.07	0.62	1.09	0.66	1.42	0.50	0.54	1.06	0.79	0.74

TABLE 3
SUMMARY OF BODY WEIGHT CHANGE DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
1-8	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.3	0.2	0.0	0.1	-0.1	0.1	0.1	0.1	0.2	0.0
	S.D.	0.42	0.26	0.34	0.22	0.33	0.24	0.15	0.10	0.17	0.08
8-15	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.4	0.2	0.2	0.0	0.4	0.1	0.1	0.1	0.1	0.0
	S.D.	0.22	0.42	0.13	0.28	0.28	0.10	0.60	0.27	0.21	0.15
15-22	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.0	-0.1	-0.1	0.2	0.0	0.2	0.2	0.1	0.2	0.1
	S.D.	0.22	0.25	0.22	0.15	0.13	0.05	0.22	0.14	0.13	0.17
22-29	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	0.1	0.2	0.1	0.3	-0.1	0.0	0.1	0.2	0.1	0.2
	S.D.	0.26	0.10	0.24	0.10	0.10	0.24	0.26	0.10	0.23	0.05
29-36	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.0	0.1	0.0	-0.1	0.1	0.1	0.2	0.0	0.0	0.0
	S.D.	0.28	0.22	0.29	0.17	0.08	0.19	0.06	0.18	0.26	0.22
36-43	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.2	0.0	0.0	0.3	0.0	0.0	0.2	0.1	0.0	0.1
	S.D.	0.39	0.10	0.13	0.14	0.21	0.24	0.28	0.22	0.27	0.17
43-50	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.1	0.0	0.0	-0.2	-0.2	0.1	-0.1	-0.1	0.0	-0.2
	S.D.	0.26	0.13	0.18	0.23	0.17	0.17	0.19	0.10	0.08	0.19
50-57	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.1	0.2	0.2	0.4	0.4	0.0	0.1	0.2	0.2	0.2
	S.D.	0.18	0.10	0.13	0.22	0.10	0.14	0.17	0.19	0.25	0.20
57-64	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.0	0.0	-0.1	-0.2	0.0	0.0	0.0	0.2	0.0	0.0
	S.D.	0.26	0.42	0.19	0.24	0.17	0.14	0.14	0.18	0.21	0.12

RTM - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES OF MALE DATA

TABLE 3
SUMMARY OF BODY WEIGHT CHANGE DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
64-71	N	4	4	4	4	4	4	4	4	4	4
RTF	MEAN	0.0	0.2	0.1	0.3	0.0	0.1	-0.1	0.1	-0.1	0.0
	S.D.	0.21	0.28	0.14	0.17	0.17	0.13	0.17	0.13	0.32	0.13
71-78	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.2	0.1	0.0	0.1	0.1	0.2	0.2	0.1	0.4	0.1
	S.D.	0.25	0.16	0.22	0.13	0.20	0.10	0.24	0.17	0.19	0.26
78-85	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.0	0.0	0.1	0.0	0.2	-0.1	0.2	0.0	0.0	0.0
	S.D.	0.13	0.24	0.31	0.32	0.19	0.15	0.22	0.15	0.14	0.10
85-92	N	4	4	4	4	4	4	4	4	4	4
	MEAN	0.0	-0.1	0.0	0.1	0.0	0.1	0.1	0.0	-0.2	0.1
	S.D.	0.17	0.25	0.21	0.24	0.41	0.21	0.15	0.26	0.21	0.22
1-92	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.3	1.1	0.5	1.1	0.9	1.2	1.3	1.1	0.9	0.6
	S.D.	0.62	0.79	0.76	0.17	0.69	0.17	0.31	0.50	0.50	0.15

RTF - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES OF FEMALE DATA

TABLE 4
SUMMARY OF FOOD CONSUMPTION DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
1-8	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.9	1.8	1.9	2.1	1.7	1.3	1.9*	1.7	1.8*	1.4
	S.D.	0.35	0.55	0.29	0.13	0.43	0.38	0.26	0.13	0.15	0.29
8-15	N	4	4	4	4	4	4	4	4	4	4
RTF	MEAN	2.1	1.7	1.8	2.1	1.9	1.6	1.8	1.8	1.9	1.5
	S.D.	0.25	0.42	0.33	0.20	0.23	0.18	0.59	0.06	0.14	0.26
15-22	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.9	1.6	1.8	2.1	1.7	1.7	1.8	1.7	1.8	1.6
	S.D.	0.24	0.29	0.39	0.22	0.26	0.14	0.29	0.24	0.13	0.25
22-29	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	1.9	1.8	1.8	2.0	1.8	1.7	1.9	1.8	2.0	1.8
	S.D.	0.13	0.39	0.53	0.08	0.08	0.17	0.14	0.13	0.26	0.19
29-36	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.9	1.7	2.0	2.0	1.8	1.7	2.0	1.9	1.8	1.7
	S.D.	0.34	0.34	0.50	0.29	0.22	0.17	0.17	0.08	0.26	0.21
36-43	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.9	1.8	2.1	2.0	1.8	1.6	2.1	2.0	2.0	1.7
	S.D.	0.42	0.38	0.29	0.21	0.33	0.13	0.26	0.10	0.32	0.30
43-50	N	4	4	4	4	4	4	4	4	4	4
	MEAN	2.1	1.8	2.0	2.0	1.7	1.8	2.2	1.9	2.0	1.8
	S.D.	0.29	0.35	0.17	0.22	0.21	0.31	0.24	0.19	0.31	0.43
50-57	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	1.7	1.7	2.0	1.9	1.8	1.6	2.0	1.9	1.7	1.6
	S.D.	0.19	0.29	0.24	0.50	0.06	0.17	0.13	0.10	0.22	0.31
57-64	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	2.1	1.9	2.1	2.2	1.8	1.6	2.2*	1.9	1.9	1.6
	S.D.	0.21	0.33	0.46	0.15	0.06	0.10	0.31	0.15	0.24	0.30

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE AT $P \geq 0.05$
RTM - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES OF MALE DATA
RTF - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES OF FEMALE DATA

TABLE 4
SUMMARY OF FOOD CONSUMPTION DATA (KG)

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

	SEX:	MALE					FEMALE				
	GROUP:	1	2	3	4	5	1	2	3	4	5
	DOSE:	0	10	50	200	1000	0	10	50	200	1000
DAY	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
64-71	N	4	4	4	4	4	4	4	4	4	4
	MEAN	2.5	2.0	2.1	2.2	1.8	1.8	1.9	2.1	1.9	1.8
	S.D.	0.71	0.30	0.22	0.37	0.25	0.24	0.32	0.12	0.26	0.28
71-78	N	4	4	4	4	4	4	4	4	4	4
	MEAN	2.0	2.0	2.1	2.2	1.8	1.9	2.0	2.2	2.2	1.8
	S.D.	0.13	0.21	0.32	0.25	0.27	0.24	0.39	0.21	0.21	0.32
78-85	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	2.1	1.8	2.1	2.2	2.1	1.8	2.3*	2.3*	2.0	1.9
	S.D.	0.15	0.52	0.35	0.28	0.29	0.30	0.26	0.22	0.21	0.24
85-92	N	4	4	4	4	4	4	4	4	4	4
	MEAN	1.9	1.7	2.0	2.0	1.8	1.6	2.0	1.9	1.7	1.6
	S.D.	0.13	0.24	0.22	0.17	0.27	0.16	0.41	0.22	0.28	0.39
1-92	N	4	4	4	4	4	4	4	4	4	4
RTM	MEAN	25.7	23.2	25.7	27.0	23.4	21.6	25.9*	24.8	24.6	21.6
	S.D.	2.46	4.03	3.99	2.34	1.55	1.54	2.18	0.94	2.30	3.03

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE AT $P \geq 0.05$
RTM - RANK TRANSFORMATION PERFORMED DURINGS STATISTICAL ANALYSES OF MALE DATA

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	RBC - MI/UL			HGB - G/DL			HCT - %			MCV - FL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.88	6.52	6.91	13.6	15.0	15.6	40.8	46.8	47.9	69.3	71.8	69.3
S.D.	.433	.334	.625	.90	1.11	1.15	2.32	2.58	4.06	1.18	1.36	.66
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.60	6.83	6.83	14.3	14.5	14.2	43.6	45.8	44.1	65.9	67.1*	64.6*
S.D.	.536	.456	.452	1.38	.95	.88	4.64	3.41	3.45	2.74	1.89	1.97
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.94	6.59	6.88	13.3	14.6	15.0	39.5	45.5	45.8	66.5	69.1	66.6
S.D.	.415	.423	.389	1.17	1.09	1.06	3.21	3.26	3.39	1.05	1.59	2.20
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.55	6.76	6.92	14.0	14.5	14.6	42.6	45.8	45.1	65.1*	67.8*	65.2*
S.D.	.408	.163	.401	.59	.76	1.01	2.17	1.90	2.74	1.33	2.12	1.23
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.53	6.96	6.77	14.1	14.9	14.2	42.3	46.6	43.7	64.8*	67.0*	64.6*
S.D.	.292	.492	.323	.67	.67	.39	2.02	2.36	.81	2.39	2.12	2.21

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	RBC - MI/UL			HGB - G/DL			HCT - %			MCV - FL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
		---RT---										
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.70	6.82	6.73	14.5	14.8	14.2	43.2	45.7	43.6	64.5	67.0	64.7
S.D.	.231	.236	.738	.92	.41	1.74	2.65	1.13	5.11	2.09	1.96	1.79
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.21	6.48	6.41	13.3	13.6	13.3	39.9	43.0	40.9	64.4	66.7	64.0
S.D.	.361	.812	.435	.24	1.12	.33	1.51	3.45	1.48	3.08	2.90	2.66
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.52	6.55	6.59	14.3	14.4	14.4	43.4	45.1	44.3	66.6	68.9	67.4
S.D.	.171	.262	.666	.29	.58	1.27	.75	1.43	3.98	1.33	1.13	.85
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.41	6.85	6.41	14.0	14.9	13.8	42.1	46.6	42.1	65.7	68.1	65.7
S.D.	.433	.073	.526	.93	.57	.99	2.54	1.91	3.11	2.22	2.45	2.69
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.77	7.02	6.48	14.9	15.5	14.3	45.0	48.2	43.3	66.5	68.8	66.8
S.D.	.433	.239	.376	.67	.81	1.16	1.57	2.36	3.31	2.10	2.44	2.51

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	MCH - PG			MCHC - G/DL			PLATELET - TH/UL			PT - S		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13 RT
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	23.1	23.0	22.5	33.3	32.1	32.6	301	281	290	6.2	6.5	6.8
S.D.	.53	.73	.44	.81	.93	.39	44.6	28.0	23.9	.14	.15	.71
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.7	21.3*	20.8*	32.9	31.7	32.1	260	250	290	6.2	6.4	6.3
S.D.	.73	.59	.82	.39	.59	.67	108.7	125.8	81.1	.15	.24	.21
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	22.3	22.1	21.8	33.5	32.0	32.8	307	322	321	6.5	6.5	6.4
S.D.	.37	.49	.61	.41	.25	.17	36.0	41.8	35.6	.40	.37	.32
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.4*	21.4*	21.1*	32.9	31.6	32.3	362	313	335	6.5	6.3	6.3
S.D.	.65	.83	.71	.61	.37	.69	101.5	67.6	76.7	.13	.21	.21
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.6*	21.4*	21.0*	33.3	31.9	32.5	320	269	299	6.3	6.3	6.2
S.D.	1.19	.83	.85	.76	.22	.39	88.5	69.6	62.5	.30	.13	.05

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	MCH - PG			MCHC - G/DL			PLATELET - TH/UL			PT - S		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
						RT				RT	RT	RT
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.6	21.8	21.1	33.6	32.4	32.6	313	264	278	7.3	7.4	7.1
S.D.	.78	.69	.80	.19	.10	.43	67.4	53.0	59.2	1.60	1.87	1.62
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.5	21.0	20.8	33.3	31.5*	32.4	294	243	297	6.4	6.4	6.3
S.D.	.94	1.04	1.20	.73	.45	1.10	28.8	54.6	50.0	.15	.24	.05
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.8	21.9	21.8	32.8	31.8*	32.4	349	298	313	7.3	6.5	6.3
S.D.	.73	.53	.30	.46	.37	.05	59.5	64.7	87.6	1.65	.22	.15
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	21.8	21.7	21.6	33.2	31.9	32.9	315	277	290	6.5	6.5	6.3
S.D.	.83	.67	.90	.28	.34	.17	44.7	31.6	33.4	.05	.37	.20
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	22.0	22.0	21.9	33.1	32.1	32.8	323	288	320	6.4	6.4	6.3
S.D.	.48	.83	.79	.34	.13	.47	38.7	41.5	26.7	.15	.24	.19

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	APTT - S WEEK -1 (RT)	APTT - S WEEK 8	APTT - S WEEK 13	FIBRIN - MG/DL WEEK -1	FIBRIN - MG/DL WEEK 8 (RT)	FIBRIN - MG/DL WEEK 13	WBC - TH/UL WEEK -1	WBC - TH/UL WEEK 8	WBC - TH/UL WEEK 13	SEG AB - TH/UL WEEK -1	SEG AB - TH/UL WEEK 8	SEG AB - TH/UL WEEK 13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.3	12.0	12.2	268	125	132	15.6	8.7	9.0	11.0	5.1	5.4
S.D.	.71	1.41	1.52	80.8	18.3	33.1	3.79	2.19	2.00	3.21	1.75	1.48
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	10.5	10.5	10.3*	199	151	173	9.5*	10.8	11.5	5.7*	6.8	7.5
S.D.	.38	.40	.29	8.6	6.0	34.1	4.02	2.59	2.84	3.05	1.45	2.05
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.2	10.6	10.7	231	190*	184	8.3*	9.7	9.4	4.7*	5.7	5.6
S.D.	.46	.51	.75	43.1	50.5	26.9	.57	1.30	1.49	.83	.85	1.01
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	10.7	10.4	10.3*	189	202*	192	12.7	13.3	10.8	7.6	8.4	6.5
S.D.	.56	.83	.78	36.8	36.7	40.2	2.82	3.80	4.35	2.20	3.01	3.32
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.0	11.1	10.9	197	177	173	9.4*	10.1	9.1	5.4*	6.0	5.1
S.D.	.26	.91	.49	69.0	91.8	62.5	1.56	3.82	1.31	1.60	3.50	1.32

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	APTT - S			FIBRIN - MG/DL			WBC - TH/UL			SEG AB - TH/UL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
							RT					
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	12.5	11.3	11.7	191	132	157	11.2	9.6	11.1	7.0	5.6	6.8
S.D.	2.00	.66	1.59	87.7	7.4	17.9	4.12	1.59	1.46	2.78	1.49	.97
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.9	11.1	11.1	162	145	149	11.2	10.9	11.4	6.6	6.8	7.3
S.D.	.87	1.20	1.00	44.7	39.2	27.4	2.35	2.89	2.22	1.27	3.16	2.20
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	14.0	11.1	11.2	122	126	145	9.3	9.6	9.2	5.8	5.9	5.4
S.D.	3.75	.75	1.06	35.7	14.1	22.1	1.48	1.03	1.05	1.56	1.11	.97
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.6	11.4	11.8	181	144	185	9.9	10.3	12.9	6.4	6.5	8.6
S.D.	1.24	1.11	1.53	100.8	22.5	36.6	2.43	1.77	2.88	2.48	1.38	2.43
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	11.9	10.9	11.1	149	144	144	9.1	8.5	8.4	5.7	5.2	5.1
S.D.	.81	.87	.80	27.8	30.6	12.8	.98	1.46	1.58	1.27	.98	1.29

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	LYMPH AB - TH/UL			MONO AB - TH/UL			EOSIN AB - TH/UL			BASO AB - TH/UL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
	RT									RT		RT
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	3.1	2.8	2.9	1.3	.4	.5	.2	.2	.2	.0	.0	.0
S.D.	.48	.31	.53	.45	.19	.25	.05	.13	.10	.05	.05	.00
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.9	3.0	3.0	.8	.6	.6	.1	.2	.3	.0	.0	.0
S.D.	1.04	.99	.60	.22	.21	.19	.10	.13	.19	.00	.05	.00
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.6	3.0	2.8	.7	.6	.6	.2	.2	.3	.0	.0	.0
S.D.	.17	.64	.51	.22	.17	.18	.10	.19	.17	.00	.06	.05
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	3.9	3.6	3.5	.8	.8	.5	.2	.3	.3	.0	.0	.0
S.D.	1.33	.75	.97	.26	.19	.15	.13	.22	.10	.05	.06	.05
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	3.0	2.9	3.1	.7	.7	.6	.2	.4	.4	.0	.0	.0
S.D.	.57	.44	.42	.27	.39	.10	.14	.24	.18	.06	.06	.05

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 5
SUMMARY OF CLINICAL HEMATOLOGY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	LYMPH AB - TH/UL			MONO AB - TH/UL			EOSIN AB - TH/UL			BASO AB - TH/UL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
				RT						RT		
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	3.3	3.2	3.4	.8	.4	.5	.1	.2	.3	.0	.0	.0
S.D.	1.06	.50	.48	.48	.27	.17	.08	.08	.22	.05	.05	.05
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	3.4	3.1	3.1	.9	.6	.6	.2	.3	.3	.0	.0	.0
S.D.	.91	.77	.48	.19	.34	.25	.05	.22	.05	.00	.06	.00
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.7	3.0	3.1	.6	.4	.4	.2	.3	.3	.0	.1	.0
S.D.	.56	.42	.64	.19	.06	.06	.17	.08	.06	.00	.05	.05
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.9	3.2	3.3	.4	.4	.6	.2	.2	.3	.0	.0	.0
S.D.	.34	.70	.13	.13	.22	.36	.08	.13	.14	.00	.06	.05
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.6	2.5	2.5	.6	.4	.4	.2	.2	.3	.0	.0	.0
S.D.	.61	.54	.29	.17	.19	.05	.05	.08	.17	.00	.05	.05

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	GLUCOSE - MG/DL			UREA N - MG/DL			CREAT - MG/DL			ALK P - U/L		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13 RT	-1	8	13	-1	8	13	-1	8	13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	97	93	100	12	15	14	.8	.8	.9	71	48	45
S.D.	6.0	3.7	2.4	1.3	2.1	2.4	.10	.12	.08	.6	8.8	7.3
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	104	93	98	12	13	13	.8	.9	.9	76	57	52
S.D.	4.9	4.3	8.4	1.6	1.4	3.1	.10	.05	.05	12.9	7.5	9.6
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	104	98	102	14	16	14	.8	.9	.9	59	41	43
S.D.	5.3	1.0	3.4	2.6	2.6	2.9	.05	.08	.14	13.6	11.0	15.5
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	99	92	99	13	16	14	.7	.9	.9	95*	67	64
S.D.	5.4	5.1	5.0	2.6	2.6	3.4	.05	.05	.10	10.6	18.0	16.4
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	97	92	98	12	16	13	.7	.8	.8	65	56	55
S.D.	10.5	8.4	1.4	1.9	5.5	2.7	.10	.06	.06	17.6	20.1	23.1

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	GLUCOSE - MG/DL			UREA N - MG/DL			CREAT - MG/DL			ALK P - U/L		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
					---RT---					---RT---		
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	98	88	93	12	14	13	.8	.9	1.0	84	54	49
S.D.	3.1	2.5	2.4	3.1	1.5	2.9	.05	.08	.10	21.4	14.9	14.1
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	95	87	89	12	16	13	.9	.9	.9	78	56	49
S.D.	3.1	6.7	8.0	2.9	2.2	2.2	.05	.06	.06	2.9	6.8	7.1
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	105	93	101	11	15	14	.8	.9	.9	85	56	50
S.D.	7.7	6.9	9.2	1.0	1.0	2.1	.05	.13	.05	7.0	10.7	9.2
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	100	90	94	11	14	13	.8	.9	.9	83	53	50
S.D.	4.9	6.4	2.5	1.7	1.3	1.3	.05	.05	.10	12.7	7.1	7.2
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	98	91	95	12	14	14	.8	.9	.9	70	53	49
S.D.	6.0	7.5	7.1	1.9	3.7	1.6	.13	.10	.05	11.9	9.9	14.1

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	AST - U/L			ALT - U/L			T PROT - G/DL			ALBUMIN - G/DL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13 RT	-1	8	13	-1	8	13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	32	47	39	32	47	44	5.5	5.5	5.8	3.6	3.7	3.8
S.D.	4.0	1.7	8.5	5.4	5.0	8.3	.41	.52	.43	.24	.31	.22
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	29	41	34	39	41	38	5.6	5.8	6.0	3.7	3.6	3.7
S.D.	4.6	5.6	4.1	17.9	12.2	10.7	.23	.13	.32	.21	.10	.34
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	36	45	44	38	45	46	5.7	6.2	6.4*	3.4	3.7	3.8
S.D.	4.2	2.8	5.4	9.3	8.8	8.2	.35	.28	.14	.17	.19	.32
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	37	47	41	40	44	45	5.7	5.7	5.9	3.7	3.6	3.8
S.D.	7.5	5.8	10.8	6.1	4.7	7.3	.34	.30	.43	.28	.22	.21
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	32	42	47	32	51	94	5.5	5.8	5.6	3.4	3.6	3.4
S.D.	7.2	3.6	15.7	3.0	9.9	69.8	.40	.47	.13	.17	.18	.17

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	AST - U/L			ALT - U/L			T PROT - G/DL			ALBUMIN - G/DL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1 RT	8	13 RT	-1	8	13	-1	8	13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	32	43	31	39	44	39	5.4	5.4	5.5	3.4	3.5	3.5
S.D.	4.6	7.2	6.5	7.1	5.3	5.6	.39	.39	.26	.17	.06	.08
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	37	50	42	31	39	33	5.5	5.6	5.9*	3.6	3.6	3.7
S.D.	.5	2.9	6.8	1.0	3.3	2.9	.32	.24	.10	.15	.06	.08
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	33	46	33	31	35	26*	5.3	5.2	5.6	3.8*	3.6	3.8*
S.D.	1.5	4.3	4.8	3.2	5.1	7.9	.19	.21	.14	.06	.13	.14
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	29	44	28	33	40	27*	5.2	5.4	5.5	3.4	3.6	3.5
S.D.	2.2	7.0	8.9	6.8	2.8	5.2	.28	.29	.21	.13	.16	.17
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	29	43	34	30	37	49	5.3	5.5	5.7	3.7*	3.7	3.6
S.D.	5.0	12.7	5.3	4.9	3.3	25.7	.14	.38	.10	.05	.10	.10

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	GLOBULIN - G/DL WEEK -1	GLOBULIN - G/DL WEEK 8	GLOBULIN - G/DL WEEK 13	A/G - RATIO WEEK -1	A/G - RATIO WEEK 8	A/G - RATIO WEEK 13	CALCIUM - MG/DL WEEK -1 RT	CALCIUM - MG/DL WEEK 8	CALCIUM - MG/DL WEEK 13	T BILI - MG/DL WEEK -1	T BILI - MG/DL WEEK 8	T BILI - MG/DL WEEK 13
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.0	1.9	2.0	1.86	1.97	1.91	10.9	10.7	11.1	.1	.1	.1
S.D.	.35	.22	.28	.340	.108	.275	.54	.61	.33	.06	.08	.13
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	1.9	2.2	2.3	1.98	1.64	1.59	11.1	10.8	11.2	.1	.0	.1
S.D.	.05	.17	.26	.099	.163	.285	.32	.14	.26	.06	.06	.05
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.3	2.5	2.6	1.51	1.49	1.51	10.8	10.8	11.3	.1	.0	.0
S.D.	.29	.46	.31	.216	.297	.286	.10	.26	.30	.00	.05	.06
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.0	2.1	2.1	1.85	1.73	1.89	10.8	10.7	11.2	.1	.1	.1
S.D.	.37	.30	.33	.459	.278	.293	.26	.42	.22	.06	.05	.06
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.1	2.1	2.2	1.66	1.72	1.59	10.7	10.5	10.8	.1	.0	.1
S.D.	.36	.45	.26	.261	.322	.257	.28	.34	.59	.00	.05	.10

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	GLOBULIN - G/DL			A/G - RATIO			CALCIUM - MG/DL			T BILI - MG/DL		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
										RT	RT	
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	2.0	1.9	2.0	1.74	1.91	1.79	10.9	10.6	10.8	.1	.0	.0
S.D.	.32	.34	.22	.255	.319	.190	.28	.22	.13	.00	.06	.06
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	1.9	2.0	2.2	1.97	1.84	1.70	11.0	10.7	10.9	.1	.0	.1
S.D.	.31	.20	.05	.314	.190	.053	.10	.24	.69	.05	.06	.00
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	1.6	1.6	1.8	2.37	2.25	2.12	10.8	10.4	10.7	.1	.0	.1
S.D.	.18	.14	.08	.276	.193	.138	.08	.34	1.06	.05	.05	.00
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	1.8	1.8	2.0	1.99	2.07	1.79	10.7	10.5	10.8	.1	.1	.1
S.D.	.33	.39	.27	.417	.591	.349	.17	.34	.60	.06	.00	.00
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	1.6	1.8	2.0	2.40	2.02	1.78	10.8	10.6	10.8	.2	.0	.1
S.D.	.19	.29	.13	.354	.269	.148	.17	.17	.65	.05	.06	.00

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	IN PHOS - MG/DL			GGT - U/L			SODIUM - MEQ/L			POTAS - MEQ/L		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
		RT							RT			
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.2	5.3	5.3	2	1	2	146	147	154	4.8	4.7	5.0
S.D.	.38	.33	.34	.8	.6	2.1	.8	.6	6.9	.52	.05	.67
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.2	5.1	5.4	2	1	3	148	147	152	4.4	4.7	4.6
S.D.	.36	.25	.49	.0	.8	2.2	1.0	1.3	1.0	.31	.29	.27
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	4.8*	5.0	5.3	2	1	3	147	147	151	4.1	5.0	4.6
S.D.	.51	.19	.17	.5	.5	2.8	2.2	1.7	3.2	.30	.59	.28
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.8	5.0	5.3	3*	3	4	147	147	152	4.6	4.6	4.6
S.D.	.48	.38	.91	.0	1.7	1.4	1.3	1.0	1.4	.26	.36	.57
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.9	5.0	5.4	2	1	3	148	148	151	4.4	4.6	4.5
S.D.	.26	.41	.66	.0	1.0	1.0	2.4	2.6	2.2	.19	.34	.22

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, $P \leq 0.05$.
RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	IN PHOS - MG/DL			GGT - U/L			SODIUM - MEQ/L			POTAS - MEQ/L		
	WEEK			WEEK			WEEK			WEEK		
	-1	8	13	-1	8	13	-1	8	13	-1	8	13
			RT	RT	RT		RT					
1 (0 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.4	5.0	5.2	2	2	4	147	147	150	4.5	4.5	4.4
S.D.	.48	.25	.24	.5	.6	1.3	.8	.6	1.0	.15	.13	.14
2 (10 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.9	5.3	5.3	3	1	4	147	146	149	4.8	4.7	4.8
S.D.	.54	.31	.29	.6	1.2	1.7	1.4	.8	1.6	.27	.35	.43
3 (50 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.0	4.9	5.4	2	2	8	148	147	151	4.6	4.6	4.4
S.D.	.17	.34	.24	.0	.5	4.9	.8	1.0	.5	.46	.06	.17
4 (200 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	5.8	4.9	5.3	2	1	6	147	147	150	4.4	4.4	4.3
S.D.	.59	.54	.62	.0	.6	2.6	1.0	.5	2.1	.15	.22	.15
5 (1000 MG/KG/DAY)												
N	4	4	4	4	4	4	4	4	4	4	4	4
MEAN	6.1	4.8	4.9	2	1	4	149	148	149	4.9	4.6	4.5
S.D.	.63	.39	.98	.5	1.0	2.6	4.7	1.3	2.1	.17	.24	.22

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
MALES

GROUP	CHLORIDE - MEQ/L WEEK -1	8	13
1 (0 MG/KG/DAY)			
N	4	4	4
MEAN	113	113	117
S.D.	.5	1.4	6.7
2 (10 MG/KG/DAY)			
N	4	4	4
MEAN	113	113	115
S.D.	1.2	2.1	1.9
3 (50 MG/KG/DAY)			
N	4	4	4
MEAN	113	114	115
S.D.	2.9	1.5	2.1
4 (200 MG/KG/DAY)			
N	4	4	4
MEAN	113	114	113
S.D.	1.3	2.5	4.2
5 (1000 MG/KG/DAY)			
N	4	4	4
MEAN	114	115	116
S.D.	3.4	2.5	3.1

TABLE 6
SUMMARY OF CLINICAL CHEMISTRY DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS
FEMALES

GROUP	CHLORIDE - MEQ/L WEEK -1 RT	8	13
1 (0 MG/KG/DAY)			
N	4	4	4
MEAN	115	114	115
S.D.	.0	1.3	1.2
2 (10 MG/KG/DAY)			
N	4	4	4
MEAN	114	114	113
S.D.	.8	.6	3.1
3 (50 MG/KG/DAY)			
N	4	4	4
MEAN	115	114	115
S.D.	1.9	1.5	1.0
4 (200 MG/KG/DAY)			
N	4	4	4
MEAN	115	114	114
S.D.	1.0	1.7	3.9
5 (1000 MG/KG/DAY)			
N	4	4	4
MEAN	116	114	114
S.D.	3.2	1.7	2.6

RT - DATA ANALYZED FOLLOWING RANK TRANSFORMATION.

TABLE 7
INCIDENCE OF MACROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	4	4	4	4	4	4	4	4	4	4
** TOP OF LIST **											
THYROID (TY)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	2	4	4	3	4	4	4	4	4	4
UNEQUALLY SIZED		2	0	0	1	0	0	0	0	0	0
LUNG (LU)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	3	4	4	4	3	3
DARK		0	0	0	0	0	0	0	0	1	0
RAISED AREA		0	0	0	0	1	0	0	0	0	0
FAILURE TO COLLAPSE		0	0	0	0	0	0	0	0	0	1
SPLEEN (SP)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	3	4	4	4
ENLARGED		0	0	0	0	0	0	1	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	2	4	4	4	4	4	4	3	4	4
GELATINOUS		1	0	0	0	0	0	0	0	0	0
SMALL		1	0	0	0	0	0	0	1	0	0
ENLARGED		1	0	0	0	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	4	4	4	4	4	0	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	3	0	0	0	0	0
SMALL		0	0	0	0	1	0	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	2	2	3	3	3
UNEQUALLY SIZED		0	0	0	0	0	1	2	1	1	0
CYST		0	0	0	0	0	0	1	0	0	0

TABLE 7
INCIDENCE OF MACROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	4	4	4	4	4	4	4	4	4	4
** FROM PREVIOUS PAGE **											
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	2	2	3	3	3
ENLARGED		0	0	0	0	0	1	0	0	0	1
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	0	1	2	2	2
WALL, THICKENED		0	0	0	0	0	4	3	2	2	2
CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	1	4	3	2	3
WALL, THICKENED		0	0	0	0	0	3	0	1	2	1
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	0	2	2	2	3
WALL, THICKENED		0	0	0	0	0	4	2	2	2	1
RAISED AREA		0	0	0	0	0	1	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	0	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	1	1	1	0	2
THICKENED		0	0	0	0	0	3	3	3	4	2

TABLE 7
INCIDENCE OF MACROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	4	4	4	4	4	4	4	4	4	4
LN, OTHER (LN)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	3	4	4	4	4	4	4	4	4	4
DARK		1	0	0	0	0	0	0	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	3	4	4	4	4	4	4	4
ADHESION		0	0	1	0	0	0	0	0	0	0

** END OF LIST **

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

BRAIN

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10025.0	74.7	0.75	1.00
	STANDARD DEV:	997.9	2.0	0.09	0.00
M 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9375.0	71.9	0.77	1.00
	STANDARD DEV:	789.0	2.7	0.09	0.00
M 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9175.0	72.8	0.80	1.00
	STANDARD DEV:	822.1	5.2	0.08	0.00
M 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10000.0	82.0	0.82	1.00
	STANDARD DEV:	812.4	8.4	0.07	0.00
M 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9675.0	80.2	0.85	1.00
	STANDARD DEV:	1565.0	4.5	0.19	0.00

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8900.0	71.5	0.81	1.00
	STANDARD DEV:	439.7	6.1	0.09	0.00
F 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9925.0	73.9	0.75	1.00
	STANDARD DEV:	618.5	2.3	0.06	0.00
F 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9350.0	80.1	0.87	1.00
	STANDARD DEV:	1109.1	3.3	0.13	0.00
F 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9150.0	71.9	0.79	1.00
	STANDARD DEV:	619.1	3.0	0.05	0.00
F 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8375.0	74.2	0.89	1.00
	STANDARD DEV:	567.9	5.1	0.05	0.00

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

SPLEEN

SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g) RT	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO RT
M 1				
NUMBER IN GROUP:	4	4	4	4
MEAN:	10025.0	24.9	0.25	0.33
STANDARD DEV:	997.9	1.8	0.02	0.03
M 2				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9375.0	25.2	0.27	0.35
STANDARD DEV:	789.0	4.5	0.03	0.07
M 3				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9175.0	21.2	0.23	0.29
STANDARD DEV:	822.1	2.6	0.02	0.02
M 4				
NUMBER IN GROUP:	4	4	4	4
MEAN:	10000.0	23.2	0.23	0.28
STANDARD DEV:	812.4	4.2	0.03	0.05
M 5				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9675.0	25.3	0.26	0.32
STANDARD DEV:	1565.0	7.4	0.04	0.10

SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F 1				
NUMBER IN GROUP:	4	4	4	4
MEAN:	8900.0	24.1	0.27	0.34
STANDARD DEV:	439.7	1.7	0.02	0.04
F 2				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9925.0	31.6	0.32	0.43
STANDARD DEV:	618.5	7.7	0.08	0.10
F 3				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9350.0	23.3	0.25	0.29
STANDARD DEV:	1109.1	4.7	0.06	0.06
F 4				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9150.0	27.3	0.30	0.38
STANDARD DEV:	619.1	7.6	0.06	0.10
F 5				
NUMBER IN GROUP:	4	4	4	4
MEAN:	8375.0	24.8	0.30	0.33
STANDARD DEV:	567.9	3.6	0.04	0.03

RT - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

TESTIS/EPIDID

SEX	DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1				
	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10025.0	17.2	0.17	0.23
	STANDARD DEV:	997.9	4.0	0.04	0.06
M	2				
	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9375.0	18.5	0.20	0.26
	STANDARD DEV:	789.0	2.4	0.02	0.03
M	3				
	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9175.0	16.0	0.18	0.22
	STANDARD DEV:	822.1	2.7	0.03	0.03
M	4				
	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10000.0	19.8	0.20	0.24
	STANDARD DEV:	812.4	2.3	0.02	0.01
M	5				
	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9675.0	17.0	0.18	0.21
	STANDARD DEV:	1565.0	2.6	0.05	0.02

SEX	DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F	1				
	NUMBER IN GROUP:	4			
	MEAN:	8900.0			
	STANDARD DEV:	439.7			
F	2				
	NUMBER IN GROUP:	4			
	MEAN:	9925.0			
	STANDARD DEV:	618.5			
F	3				
	NUMBER IN GROUP:	4			
	MEAN:	9350.0			
	STANDARD DEV:	1109.1			
F	4				
	NUMBER IN GROUP:	4			
	MEAN:	9150.0			
	STANDARD DEV:	619.1			
F	5				
	NUMBER IN GROUP:	4			
	MEAN:	8375.0			
	STANDARD DEV:	567.9			

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

KIDNEY

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	10025.0	52.0	0.52	0.70
		STANDARD DEV:	997.9	7.6	0.03	0.12
M	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9375.0	45.9	0.49	0.64
		STANDARD DEV:	789.0	3.5	0.03	0.05
M	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9175.0	47.4	0.51	0.66
		STANDARD DEV:	822.1	7.8	0.05	0.13
M	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	10000.0	49.3	0.49	0.61
		STANDARD DEV:	812.4	6.2	0.06	0.11
M	5	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9675.0	53.2	0.55	0.67
		STANDARD DEV:	1565.0	14.1	0.08	0.19
F	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8900.0	40.5	0.46	0.57
		STANDARD DEV:	439.7	2.0	0.02	0.07
F	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9925.0	45.7	0.46	0.62
		STANDARD DEV:	618.5	3.2	0.03	0.03
F	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9350.0	40.6	0.44	0.51
		STANDARD DEV:	1109.1	2.0	0.03	0.04
F	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9150.0	41.6	0.46	0.58
		STANDARD DEV:	619.1	4.5	0.04	0.08
F	5	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8375.0	40.8	0.49	0.55
		STANDARD DEV:	567.9	5.9	0.06	0.09

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

THYMUS

SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g) RT	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO RT
M 1				
NUMBER IN GROUP:	4	4	4	4
MEAN:	10025.0	11.79	0.113	0.160
STANDARD DEV:	997.9	7.65	0.064	0.107
M 2				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9375.0	9.99	0.105	0.139
STANDARD DEV:	789.0	3.42	0.031	0.047
M 3				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9175.0	9.93	0.106	0.136
STANDARD DEV:	822.1	4.13	0.038	0.055
M 4				
NUMBER IN GROUP:	4	4	4	4
MEAN:	10000.0	12.87	0.127	0.156
STANDARD DEV:	812.4	3.14	0.023	0.031
M 5				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9675.0	12.93	0.135	0.161
STANDARD DEV:	1565.0	2.85	0.035	0.035

SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F 1				
NUMBER IN GROUP:	4	4	4	4
MEAN:	8900.0	8.71	0.097	0.124
STANDARD DEV:	439.7	3.43	0.034	0.059
F 2				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9925.0	13.87	0.139	0.188
STANDARD DEV:	618.5	1.86	0.012	0.024
F 3				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9350.0	8.67	0.092	0.110
STANDARD DEV:	1109.1	2.98	0.023	0.043
F 4				
NUMBER IN GROUP:	4	4	4	4
MEAN:	9150.0	9.88	0.107	0.136
STANDARD DEV:	619.1	3.20	0.032	0.040
F 5				
NUMBER IN GROUP:	4	4	4	4
MEAN:	8375.0	9.89	0.118	0.133
STANDARD DEV:	567.9	1.17	0.009	0.014

RT - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

OVARY

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4			
		MEAN:	10025.0			
		STANDARD DEV:	997.9			
M	2	NUMBER IN GROUP:	4			
		MEAN:	9375.0			
		STANDARD DEV:	789.0			
M	3	NUMBER IN GROUP:	4			
		MEAN:	9175.0			
		STANDARD DEV:	822.1			
M	4	NUMBER IN GROUP:	4			
		MEAN:	10000.0			
		STANDARD DEV:	812.4			
M	5	NUMBER IN GROUP:	4			
		MEAN:	9675.0			
		STANDARD DEV:	1565.0			
F	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8900.0	1.36	0.015	0.019
		STANDARD DEV:	439.7	0.27	0.003	0.003
F	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9925.0	2.04	0.020	0.028
		STANDARD DEV:	618.5	1.56	0.016	0.021
F	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9350.0	1.19	0.013	0.015
		STANDARD DEV:	1109.1	0.56	0.007	0.007
F	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9150.0	1.15	0.013	0.016
		STANDARD DEV:	619.1	0.49	0.006	0.008
F	5	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8375.0	1.26	0.015	0.017
		STANDARD DEV:	567.9	0.77	0.009	0.011

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ADRENAL

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	10025.0	0.98	0.010	0.013
		STANDARD DEV:	997.9	0.10	0.000	0.002
M	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9375.0	0.95	0.010	0.013
		STANDARD DEV:	789.0	0.23	0.002	0.003
M	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9175.0	0.99	0.011	0.014
		STANDARD DEV:	822.1	0.24	0.002	0.003
M	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	10000.0	0.97	0.010	0.012
		STANDARD DEV:	812.4	0.12	0.001	0.002
M	5	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9675.0	0.97	0.010	0.012
		STANDARD DEV:	1565.0	0.19	0.002	0.003
F	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8900.0	1.06	0.012	0.015
		STANDARD DEV:	439.7	0.11	0.002	0.002
F	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9925.0	1.10	0.011	0.015
		STANDARD DEV:	618.5	0.12	0.001	0.002
F	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9350.0	1.12	0.012	0.014
		STANDARD DEV:	1109.1	0.14	0.002	0.002
F	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	9150.0	1.01	0.011	0.014
		STANDARD DEV:	619.1	0.09	0.000	0.001
F	5	NUMBER IN GROUP:	4	4	4	4
		MEAN:	8375.0	1.02	0.012	0.014
		STANDARD DEV:	567.9	0.29	0.003	0.003

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

LIVER/GALLBLADD

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10025.0	247	2.5	3.3
	STANDARD DEV:	997.9	29	0.2	0.5
M 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9375.0	225	2.4	3.1
	STANDARD DEV:	789.0	39	0.4	0.5
M 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9175.0	226	2.5	3.1
	STANDARD DEV:	822.1	17	0.3	0.4
M 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10000.0	244	2.4	3.0
	STANDARD DEV:	812.4	19	0.1	0.2
M 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9675.0	250	2.6	3.1
	STANDARD DEV:	1565.0	52	0.3	0.8

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8900.0	213	2.4	3.0
	STANDARD DEV:	439.7	9	0.1	0.3
F 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9925.0	233	2.3	3.2
	STANDARD DEV:	618.5	27	0.2	0.5
F 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9350.0	187	2.0*	2.3*
	STANDARD DEV:	1109.1	11	0.2	0.2
F 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9150.0	214	2.3	3.0
	STANDARD DEV:	619.1	18	0.2	0.2
F 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8375.0	221	2.6	3.0
	STANDARD DEV:	567.9	19	0.2	0.3

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE AT $P \geq 0.05$

TABLE 8
SUMMARY OF ORGAN WEIGHT DATA

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

THYROID/PARATHYR

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
			RT	RT	
M 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10025.0	0.92	0.009	0.012
	STANDARD DEV:	997.9	0.24	0.002	0.003
M 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9375.0	0.75	0.008	0.010
	STANDARD DEV:	789.0	0.09	0.001	0.002
M 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9175.0	1.13	0.012	0.015
	STANDARD DEV:	822.1	0.52	0.005	0.006
M 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	10000.0	0.86	0.009	0.010
	STANDARD DEV:	812.4	0.16	0.001	0.001
M 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9675.0	0.75	0.008	0.009
	STANDARD DEV:	1565.0	0.19	0.001	0.003

SEX DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F 1	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8900.0	0.81	0.009	0.011
	STANDARD DEV:	439.7	0.14	0.002	0.002
F 2	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9925.0	0.85	0.009	0.012
	STANDARD DEV:	618.5	0.26	0.002	0.003
F 3	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9350.0	0.72	0.008	0.009
	STANDARD DEV:	1109.1	0.16	0.002	0.002
F 4	NUMBER IN GROUP:	4	4	4	4
	MEAN:	9150.0	0.81	0.009	0.011
	STANDARD DEV:	619.1	0.14	0.002	0.002
F 5	NUMBER IN GROUP:	4	4	4	4
	MEAN:	8375.0	0.73	0.009	0.010
	STANDARD DEV:	567.9	0.10	0.001	0.001

RT - RANK TRANSFORMATION PERFORMED DURING STATISTICAL ANALYSES

TABLE 9
INCIDENCE OF MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	4	4	4	4	4	4	4	4	4	4
** TOP OF LIST **											
PITUITARY (PI)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	4	3	0	0	0	4
--CYST		0	0	0	0	0	1	0	0	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	4	3	0	0	0	4
--VACUOLAR DEGENERATION		0	0	0	0	0	1	0	0	0	0
LUNG (LU)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	2	0	0	0	1	2	0	0	0	0
--PERIBRONCHIAL/PERIVASCULAR, INFILTRATION, LYMPHOID		2	0	0	0	1	1	0	0	0	4
--ALVEOLUS, MACROPHAGES, VACUOLATED		1	0	0	0	0	0	0	0	0	0
--PNEUMONIA, INTERSTITIAL		1	0	0	0	1	2	0	0	0	1
--CONGESTION		0	0	0	0	1	0	0	0	0	0
--GRANULOMATOUS INFLAMMATION, SUBPLEURAL		0	0	0	0	1	0	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--INFLAMMATION		4	4	4	4	4	4	4	4	4	4
--HEPATOCELLULAR DEGENERATION/NECROSIS		0	0	0	0	4	0	0	0	0	3
--PERIPORTAL FIBROSIS		0	0	0	0	1	0	0	0	0	1
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED		0	0	0	1	0	0	0	0	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	1	0	0	0	1	2	0	0	0	0
--LYMPHOID INFILTRATE		3	0	0	0	3	2	0	0	0	4

TABLE 9
INCIDENCE OF MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	4	4	4	4	4	4	4	4	4	4
STOMACH, GL (ST)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--LYMPHOID INFILTRATE		4	0	0	0	4	4	0	0	0	4
--INFLAMMATION, VASCULAR		0	0	0	0	1	0	0	0	0	0
DUODENUM (DU)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	3	0	0	0	1	0	0	0	0	3
--CRYPT ABSCESS		1	0	0	0	3	4	0	0	0	1
PANCREAS (PA)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	2	0	0	0	4	3	0	0	0	4
--ATROPHY		1	0	0	0	0	0	0	0	0	0
--INCREASED APOPTOSIS		1	0	0	0	0	1	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	3	4	0	0	0	4
--ATROPHY		0	0	0	0	1	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	4	0	0	0	4	0	0	0	0	0
	NOT REMARKABLE:	3	0	0	0	4	0	0	0	0	0
--INFLAMMATION		1	0	0	0	0	0	0	0	0	0
^DEATH COMMENT (DC)	NUMBER EXAMINED:	3	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	0	0	0	0	1	0	0	0	0	0
--SCHEDULED SACRIFICE		3	0	0	0	3	4	0	0	0	4

TABLE 9
INCIDENCE OF MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	4	4	4	4	4	4	4	4	4	4
LN, OTHER (LN)	NUMBER EXAMINED:	1	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--CONGESTION		1	0	0	0	0	0	0	0	0	0

** END OF LIST **

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN/TISSUE EXAMINED	NUMBER:	4	4	4	4	4	4	4	4	4	4
** TOP OF LIST **											
PITUITARY (PI)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	4	3	0	0	0	4
--CYST	->	4	0	0	0	4	3	0	0	0	4
	P>	0	0	0	0	0	1	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	4	3	0	0	0	4
--VACUOLAR DEGENERATION	->	4	0	0	0	4	3	0	0	0	4
	2>	0	0	0	0	0	1	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN/TISSUE EXAMINED	--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:	----------MALE---------					---------FEMALE--------				
GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:	4	4	4	4	4	4	4	4	4	4
LUNG (LU) ..... NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
NOT REMARKABLE:	2	0	0	0	1	2	0	0	0	0
--PERIBRONCHIAL/PERIVASCULAR, INFILTRATION, LYMPHOID ->	2	0	0	0	3	3	0	0	0	0
1>	2	0	0	0	1	1	0	0	0	4
TL>	4	0	0	0	4	4	0	0	0	4
MN>	0.5	0.0	0.0	0.0	0.3	0.3	0.0	0.0	0.0	1.0
--ALVEOLUS, MACROPHAGES, VACUOLATED ->	3	0	0	0	4	4	0	0	0	4
1>	1	0	0	0	0	0	0	0	0	0
TL>	4	0	0	0	4	4	0	0	0	4
MN>	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
--PNEUMONIA, INTERSTITIAL ->	3	0	0	0	3	2	0	0	0	3
1>	1	0	0	0	1	2	0	0	0	1
TL>	4	0	0	0	4	4	0	0	0	4
MN>	0.3	0.0	0.0	0.0	0.3	0.5	0.0	0.0	0.0	0.3
--CONGESTION ->	4	0	0	0	3	4	0	0	0	4
3>	0	0	0	0	1	0	0	0	0	0
TL>	4	0	0	0	4	4	0	0	0	4
MN>	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0
--GRANULOMATOUS INFLAMMATION, SUBPLEURAL ->	4	0	0	0	3	4	0	0	0	4
2>	0	0	0	0	1	0	0	0	0	0
TL>	4	0	0	0	4	4	0	0	0	4
MN>	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN/TISSUE EXAMINED		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	4	4	4	4	4	4	4	4	4	4
LIVER (LI)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--INFLAMMATION	1>	4	4	4	4	1	4	3	4	4	1
	2>	0	0	0	0	1	0	1	0	0	1
	3>	0	0	0	0	2	0	0	0	0	2
	TL>	4	4	4	4	4	4	4	4	4	4
	MN>	1.0	1.0	1.0	1.0	2.3	1.0	1.3	1.0	1.0	2.3
--HEPATOCELLULAR DEGENERATION/NECROSIS	->	4	4	4	4	0	4	4	4	4	1
	1>	0	0	0	0	1	0	0	0	0	1
	2>	0	0	0	0	1	0	0	0	0	2
	3>	0	0	0	0	2	0	0	0	0	0
	TL>	4	4	4	4	4	4	4	4	4	4
	MN>	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	1.3
--PERIPORTAL FIBROSIS	->	4	4	4	4	3	4	4	4	4	3
	1>	0	0	0	0	0	0	0	0	0	1
	2>	0	0	0	0	1	0	0	0	0	0
	TL>	4	4	4	4	4	4	4	4	4	4
	MN>	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.3
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	->	4	4	4	3	4	4	4	4	4	4
	2>	0	0	0	1	0	0	0	0	0	0
	TL>	4	4	4	4	4	4	4	4	4	4
	MN>	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN/TISSUE EXAMINED	NUMBER:	4	4	4	4	4	4	4	4	4	4
GALLBLADDER (GB)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	1	0	0	0	1	2	0	0	0	0
--LYMPHOID INFILTRATE	->	1	0	0	0	1	2	0	0	0	0
	1>	3	0	0	0	3	2	0	0	0	4
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.8	0.0	0.0	0.0	0.8	0.5	0.0	0.0	0.0	1.0
STOMACH, GL (ST)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--LYMPHOID INFILTRATE	1>	2	0	0	0	1	1	0	0	0	0
	2>	2	0	0	0	3	3	0	0	0	4
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	1.5	0.0	0.0	0.0	1.8	1.8	0.0	0.0	0.0	2.0
--INFLAMMATION, VASCULAR	->	4	0	0	0	3	4	0	0	0	4
	1>	0	0	0	0	1	0	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN/TISSUE EXAMINED	NUMBER:	4	4	4	4	4	4	4	4	4	4
DUODENUM (DU)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	3	0	0	0	1	0	0	0	0	3
--CRYPT ABSCESS	->	3	0	0	0	1	0	0	0	0	3
	1>	1	0	0	0	2	4	0	0	0	0
	2>	0	0	0	0	1	0	0	0	0	1
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.3	0.0	0.0	0.0	1.0	1.0	0.0	0.0	0.0	0.5
PANCREAS (PA)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	2	0	0	0	4	3	0	0	0	4
--ATROPHY	->	3	0	0	0	4	4	0	0	0	4
	2>	1	0	0	0	0	0	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
--INCREASED APOPTOSIS	->	3	0	0	0	4	3	0	0	0	4
	2>	1	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	1	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.5	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0

TABLE 10
INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS

90-DAY ORAL (CAPSULE) TOXICITY STUDY WITH TKA 40082 IN DOGS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN/TISSUE EXAMINED	NUMBER:	4	4	4	4	4	4	4	4	4	4
THYMUS (TH)	NUMBER EXAMINED:	4	0	0	0	4	4	0	0	0	4
	NOT REMARKABLE:	4	0	0	0	3	4	0	0	0	4
--ATROPHY	->	4	0	0	0	3	4	0	0	0	4
	2>	0	0	0	0	1	0	0	0	0	0
	TL>	4	0	0	0	4	4	0	0	0	4
	MN>	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0
PROSTATE (PR)	NUMBER EXAMINED:	4	0	0	0	4	0	0	0	0	0
	NOT REMARKABLE:	3	0	0	0	4	0	0	0	0	0
--INFLAMMATION	->	3	0	0	0	4	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0
	TL>	4	0	0	0	4	0	0	0	0	0
	MN>	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LN, OTHER (LN)	NUMBER EXAMINED:	1	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--CONGESTION	3>	1	0	0	0	0	0	0	0	0	0
	TL>	1	0	0	0	0	0	0	0	0	0
	MN>	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

** END OF LIST **

APPENDIX 1

Protocol
Protocol Amendments
Protocol Deviations

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Sponsor:

Additives Division
Ciba Specialty Chemicals Corporation
Tarrytown, NY 10591-9005

PROTOCOL

Study Title:

90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Date:

July 16, 1998

Performing Laboratory:

Covance Laboratories Inc.
9200 Leesburg Pike
Vienna, Virginia 22182-1699

Laboratory Study Identification:

Proposal No. 23109B

Covance Project No. 6623-117

Study
90-Day Oral (Capsule) Toxicity Study with TKA 40082 in Dogs

Purpose
To evaluate the toxicity of TKA 40082 when administered daily by capsule to dogs for at least 90 days.

Sponsor
Additives Division
Ciba Speciality Chemicals Corporation
540 White Plains Rd.
P.O. Box 2005
Tarrytown, NY 10591-9005

Study Monitor
Richard Balcomb
Additives Division
Ciba Speciality Chemicals Corporation
Phone No.: 914.785.4496
Facsimile No.: 914.785.4147

Study Location
Covance Laboratories Inc.
9200 Leesburg Pike
Vienna, Virginia 22182-1699

Study Director
Marie E. McKeon, MPhil., DABT
Covance Laboratories Inc.
Phone No.: 703.893.5400
Facsimile No.: 703.759.6947

Toxicologist
Sharon P. Dyke, BS
Covance Laboratories Inc.

Proposed Study Timetable
In-Life Start Date: August 5, 1998
In-Life End Date: November 5, 6 and 9, 1998
Audited Draft Report Date: February, 1999

Regulatory Compliance
This study will be conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the US Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with the Organisation for Economic Co-operation and Development revised Principles of Good Laboratory Practice [C(97)186/Final] and any applicable amendments.

Regulatory Guideline(s)
This study design is based on US FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives used in Food (1982) and with OECD Guidelines (1981) for the testing of chemicals, Section 4, Health Effects, No. 409.

Animal Care and Use Statement
All procedures in this protocol are in compliance with the Animal Welfare Act Regulations, 9 CFR 1-4. In the opinion of the Sponsor and Study Director, the study does not unnecessarily duplicate any previous work.

Quality Assurance
The protocol, study conduct, and final report will be audited by the Covance Laboratories Inc. (Covance) Quality Assurance Unit (QAU).

Test Material

Identification
TKA 40082

Lot Number
The lot number will be maintained in the raw data.

Purity
Responsibility of the Sponsor

Stability
Responsibility of the Sponsor

Storage Conditions
Room temperature, protect from light.

Characteristics
Information on synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor.

Control Material

Identification
Gelatin Capsule

Storage Conditions
At room temperature

Characteristics
Information on synthesis methods, composition, or other characteristics that define the control material is on file with the manufacturer.

Reserve (Archive) Samples
A reserve sample of each lot of test material (5 g) and control material (1 capsule) will be taken and stored at room temperature. These samples will be archived by Covance after completion of the in-life phase.