5. For the aforementioned reasons (# 2, 3, & 4), the data from studies T93008 and T93009 should be considered as invalid and not supportive for the sponsor's contention that selection of F-344 strain rats in place of SD strain rats for the carcinogenicity study and the practice of restricted feeding regimen are appropriate.

6. A comparison of the tumor incidences in the concurrent controls of the rat (F-344) carcinogenicity study (Report # 91/EIS011/1215) and the strain controls of Charles-River Laboratories, indicate a generally decreased incidence of tumors (pancreatic islet cell adenoma and carcinoma, thyroid follicular cell adenoma, pituitary adenoma and carcinoma, uterine endometrial stromal polyps and adenocarcinoma).

/S/ 8/17/93

Jasti B. Choudary, Ph.D., B.V.Sc.
Supervisory Pharmacologist
August 17, 1993

3-Month Oral (gavage) Toxicity Study in Rats (Study # R31193, R31293, R01994)

Testing Laboratories: [redacted]

Study Started: November 15, 1993

Study Completed: September 1, 1994

GLP Requirements: A Statement of Compliance with GLP Regulations was included.

Animals: 6-8 weeks old Sprague-Dawley (SD/Tac) male (202.9 ± 10.0 g) and female (160.8 ± 8.7 g) rats.

Drug Batch No.: 13051304

Methods: Groups of rats (10/sex/group) were given orally (gavage) E3810 (adjusted to pH 10 with 0.05 M $NaHCo_3$) at daily doses of 25, 60, 130 and 300 mg/kg/day for 3 months. The control group animals received the vehicle (0.05 M $NaHCO_3$ pH 10) in similar fashion. The volume of administration was fixed at 5 ml/kg. Additionally 42 rats/sex/dose group (6 rats/sex in the control group) were also included in the study as satellite groups and treated in similar fashion for collecting toxicokinetic data. Rats were fed ad libitum during the study period. All animals were observed daily for clinical signs and mortality. Body weights and food consumptions were recorded pre-test and weekly during the treatment phase. Just before sacrifice, blood samples were collected from abdominal aorta of overnight fasted rats for hematology and clinical chemistry tests. On day 84 of the study, 16 hour urine samples were also collected from 5 rats/sex/group for urinalysis. At the end of treatment period all animals were sacrificed and subjected to complete necropsy and histopathological examinations. Stomach slides were stained with hematoxylin and eosin and chromogranin for assessing neuroendocrine cells. Additionally, a portion of the liver from 5 rats/sex/group were used to determine hepatic enzyme induction parameters. Blood samples were collected from 3 rats/sex/group/time point from the satellite groups for measuring plasma concentration of the drug and its metabolites (desmethyl-, thioether- and desmethyl-thioether- of E 3810). The time points were 15, 30, 60 90 min., 2 and 4 hour after the drug administration on day 29 and 92 of treatment. Gastrin levels were also monitored at 4 and 24 hour after drug administration on 1, 29 and 92 of the study.

Results:

1. Observed Effects: Dose related increase in salivation was seen in treated rats.

2. Mortality: One male treated with 130 mg/kg/day died on day 55 of the study. Additionally, 2 males and 1 female of satellite groups treated with 300 mg/kg/day died during the first 2 weeks of the study period. These deaths were considered not to be treatment related.

3. Body Weight/Food Consumption/Water Consumption: Body weight gains in males were not affected by the treatment (control: mean initial body weight = 206.4 g and mean final body weight = 464.9). However, in females, body weight gains were reduced by 11%, 13%, 8% and 12% at 25, 60, 130 and 300 mg/kg/day dose levels (control: mean initial body weight = 158.9 g and mean final body weight = 305.5 g). Treatment had no significant effect on food consumptions in rats of both sexes (control: mean daily food consumptions were 22.4 g/rat/day for males and 17.8 g/rats/day for females).

4. Hematology/Coagulation/Bone Marrow: Significant increases in leukocyte (42%), lymphocyte (36%) and neutrophil (120%) counts were seen in males treated with 300 mg/kg/day.

5. Blood Chemistry/Urinalysis: At the end of treatment period, increases in serum total bilirubin (42-50%) and cholesterol (27-36%) and decreases in serum alanine transaminase (SGPT: 21-30%) and alkaline phosphatase (ALP: 13-16%) activities were seen in 300 mg/kg/day treated rats of both sexes. Additionally, serum creatinine levels were increased by 15% in 130 and 300 mg/kg/day treated males. In females, cholesterol levels were also increased (28%) in 130 mg/kg/day treated rats. Urinary pH was decreased in high dose treated males (7.2 versus 8.4 in controls).

6. Serum Gastrin Levels: Serum gastrin levels at 4 hour after drug administration on day 29 of the study, increased dose dependently. At 24 hour after drug administration on day 29, serum gastrin levels returned close to baseline in 25 and 60 mg/kg/day treated rats, but was still elevated in 130 and 300 mg/kg/day treated males and females. Similar results were seen at the end of 3-months of treatment.

Mean Serum Gastrin (pg/ml) After 1 Month of [redacted] 307640 Treatment				
Dose (mg/kg)	Hour 4		Hour 24	
	M	F	M	F
0	393	81	312.0	96
25	432	237	270.3	154
60	688*	305	310.7	189
130	906*	662*	722.7*	307
300	833*	992*	902.0*	436*

* = P ≤.05, two tailed trend on raw data

7. Plasma Levels of E 3810 and its Metabolites: The standard deviations for the plasma levels of E3810 and its metabolites are very large, hence, data is not that robust. However, the level of E3810 and its thioether metabolite increased with increasing dosage. The data also indicated that the levels of parent drug as well as its metabolites (mainly E3810 thioether) decreased after multiple dosing.

Plasma Levels (AUC_{0-t}: ng.hr/ml) of E 3810 and its Metabolites						
Dose	Day 1		Day 29		Day 92	
	Male	Female	Male	Female	Male	Female
25 mg/kg/day						
E 3810	94.8	10.1	138.1	39.9	213.6	65.2
E 3810 Desmethyl thioether	140.3	117.9	132.8	46.2	139.5	86.4
E 3810 Desmethyl	0.0	32.6	22.9	6.4	18.8	0.0
E 3810 Sulfone	0.0	0.0	0.0	0.0	0.0	0.0
E 3810 Thioether	433.2	1145.7	442.1	692.5	442.4	938.9
60 mg/kg/day						
E 3810	415.0	107.4	191.7	321.8	213.1	320.2
E 3810 Desmethyl thioether	371.3	211.1	142.2	157.5	230.1	177.5
E 3810 Desmethyl	469.6	9.7	28.7	25.0	6.5	9.1
E 3810 Sulfone	328.6	0.0	6.0	0.0	0.0	0.0
E 3810 Thioether	1504.7	2012.5	628.4	1899.3	1014.8	1864.1
130 mg/kg/day						
E 3810	379.4	262.2	371.1	387.5	439.3	585.9
E 3810 Desmethyl thioether	418.9	298.3	267.8	198.6	284.2	254.4
E 3810 Desmethyl	82.6	39.1	42.1	37.6	33.9	20.5
E 3810 Sulfone	29.2	7.7	16.2	5.9	8.7	0.0
E 3810 Thioether	1773.3	3630.7	1060.8	2370.4	1167.5	3385.7
300 mg/kg/day						
E 3810	1521.2	3509.3	839.6	2132.2	1245.8	2917.0
E 3810 Desmethyl thioether	634.0	377.1	301.5	234.9	326.5	332.2
E 3810 Desmethyl	253.3	317.3	89.3	176.2	123.5	162.8
E 3810 Sulfone	45.9	36.9	17.3	11.0	25.1	27.0
E 3810 Thioether	3203.7	5088.2	1649.0	3418.3	1712.7	5532.8

8. Hepatic Drug Metabolizing Enzyme Activities:

Effects on Hepatic Enzymes
(Percent Change From Control Values)

Parameters	25 mg/kg/day		60 mg/kg/day		130 mg/kg/day		300 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
Cytochrome P450	---	---	---	---	+12	+29	+11	+49
Cytochrome b_5	---	---	---	---	+35	+63	+66	+126
EROD	+70	+94	+191	+227	+328	+342	+288	+545
BND	---	---	---	---	---	---	---	---
END	---	---	---	---	-15	---	-29	---
TGT	---	---	+19	+40	+41	+53	+66	+87

EROD = 7-Ethoxyresorufin-O-Deethylase
BND = Benzphetamine N-Demethylase
END = Erythromycin-N-Demethylase
TGT = Thyroxin UDP-glucuronosyl transferase
- = No significant change was seen

Cytochrome P450 content was slightly increased in 130 and 300 mg/kg/day treated rats. Cytochrome b_5 content was significantly increased in rats treated with 130 and 300 mg/kg/day dose levels (male: 35-66% and females: 63-126%). Dose related increase in 7-Ethoxyresorufin-o-deethylase activity (P450 IA dependent activity) was seen in treated rats of both sexes. END activity (P450 IIIA dependent activity) was slightly reduced (15-29%) in 130 and 300 mg/kg/day treated males. BND activity which is dependent on P450 IIB was not affected by the treatment. At 60 mg/kg/day and higher dose levels, the thyroxin UDP-glucuronosyl transferase activity was increased dose dependently (males: 19-66% and females: 40-87%).

9. Organ Weights: Dose related increases in the absolute weights of kidney, liver, heart, spleen, thyroid and stomach were seen in treated rats of both sexes, while thymus weights were decreased dose dependently in treated rats of both sexes.

Effects on Organ Weights
(Percent Change from Control Values)

Organ	25 mg/kg/day		60 mg/kg/day		130 mg/kg/day		300 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
Kidneys	4	2	16	2	24	17	39	26
Liver	11	3	21	7	39	24	60	44
Heart	2	0	5	-1	6	3	9	7
Spleen	-3	-5	11	6	22	12	29	17
Thyroid	12	4	16	-2	48	21	94	42
Stomach	15	20	39	38	48	47	52	65
Thymus	-41	-28	-57	-38	-60	-44	-71	-56

10. Gross Pathology: Enlarged thyroid was seen in 3 out of 9 and 5 out of 10 rats treated with 130 and 300 mg/kg/day respectively. No other treatment related effects were seen.

11. Histopathology: Histopathological examinations revealed increased incidences of multi-focal basophilic cortical tubular regeneration in the kidney, follicular cell hypertrophy in the thyroid, eosinophilic chief cell in the glandular stomach and ECL cell hyperplasia in the stomach (fundus). The incidences of these findings are as follows:

Number of Rats With Histopathological Findings

	Sex (M/F)	Control	25 mg/kg	60 mg/kg	130 mg/kg	300 mg/kg
Number Examined		10	10	10	10	10
Kidney						
Moderate Multifocal Basophilic Cortical Tubular Regeneration	M	0	1	4	8	10
	F	0	0	0	3	10
Thyroid						
Follicular Cell Hypertrophy (minimal - slight)	M	1	2	2	5	8
	F	0	0	1	2	8
Stomach						
Eosinophilic Chief Cells (fundus: slight - moderate)	M	0	4	8	8	10
	F	0	0	7	4	10
ECL Cell Hyperplasia (fundus: moderate - marked)	M	0	8	9	6	8
	F	0	1	5	8	9

12. Morphometric Evaluation of Stomach: Dose related increases in the volume of the glandular and non-glandular stomach, thickness of gastric mucosa, ECL cell hypertrophy and ECL cell hyperplasia were seen in treated rats.

The data indicated that kidney, thyroid and stomach are the target organs of toxicities. Additionally, drug also produced dose related increases in the weights of liver, spleen and decrease in thymus weight without any histopathological changes. In this study, a no effect dose was not established. Apart from effects on gastrointestinal tract, a dose of 25 mg/kg/day (lowest tested dose) produced moderate multifocal basophilic cortical tubular regeneration in kidneys (1/10) and follicular cell hypertrophy in thyroid (2/10) in male rats. This dose level can be considered as a maximum tolerated dose (MTD) in male rats. In females, apart from effects on gastrointestinal tract, a dose of 60 mg/kg/day produced follicular cell hypertrophy in thyroid (1/10) along with 13% reductions in body weight gains. Hence, the MTD in female rats would be around 60 mg/kg/day.

FDA CDER CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) RODENT CARCINOGENICITY FACTSHEET

NDA: 20,973
CAS #:
DIVISION(s): HFD-180
DRUG NAME(S): Rabeprazole / Aciphex / E3810
SPONSOR: Eisai Inc.
LABORATORY:
P/T REVIEWER(s): Ke Zhang, Ph.D.
P/T REVIEW DATE: December 15, 1998
CARCINOGENICITY STUDY REPORT DATE: September 29, 1997

THERAPEUTIC CATEGORY: Gastric antisecretory agent

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Gastric parietal cell H^+/K^+-ATPase (proton pump) inhibitor.

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (Y/N; Date): The dose selection was based on findings from the 3-month oral (gavage) toxicity study in rats. In this study, MTD was identified at 25 mg/kg/day for males and 60 mg/kg/day for females. The doses of 7.5, 15 and 30 mg/kg/day for male and 15, 30 and 60 mg/kg/day for females were recommended by the Division and CAC Executive Committee. However, sponsor instead chose the doses of 5, 15 30 and 60 mg/kg/day for males and 5, 15, 30, 60 and 120 mg/kg/day for females.

MUTAGENIC/GENOTOXIC (Y/N/EQUIVOCAL/Na; assay): Positive in Ames tests, CHO/HGPRT forward gene mutation assay and gene forward mutation assays at TK locus in L5178Y mouse lymphoma cells.

RAT CARCINOGENICITY STUDY (multiple studies? Std1, Std2 etc):

RAT STUDY DURATION (weeks): 104 weeks for both males and females
STUDY STARTING DATE: January 23, 1995
STUDY ENDING DATE: September 29, 1997
RAT STRAIN: Sprague-Dawley (SD/Tac) rats
ROUTE: Oral gavage
DOSING COMMENTS: The pH of dose solution was adjusted to ~10.0 using 0.05 M sodium bicarbonate.

No. RAT in control (C1): 70m, 60f
Low Dose (LD): 70m, 60f
High Dose1 (HD1): 70m, 60f

Control2 (C2): 70m, 60f
Mid Dose (MD): 70m, 60f
High Dose2 (HD2): 70m, 60f

RAT Dose Levels (mg/kg/day)

RAT Low Dose: 5 (MF)
RAT Mid Dose: 15 (MF)
RAT High Dose1: 30 (MF)
RAT High Dose2: 60 (MF)
120 mg/kg/day was given to females only

Basis for doses selected (MTD, AUC ratio, saturation, maximum feasible): MTD

RAT CARCINOGENICITY (negative, positive, MF, M, F): Positive (F)

RAT TUMOR FINDINGS: The treatment produced carcinoid tumors (malignant and benign) in the stomach in females (0, 0, 1, 3, 6, 5 and 7 in the control1, control2, 5, 15, 30, 60 and 120 mg/kg groups, respectively).

RAT STUDY COMMENTS: In the 2-year oral carcinogenicity study in rats, rats (70 males/group or 60 females/group) were treated with rabeprazole by oral gavage at 0, 0, 5, 15, 30 and 60 mg/kg/day (males) or 0, 0, 5, 15, 30, 60 and 120 mg/kg/day (females) for 2 years. The dose selection was based on findings from the 3 month oral (gavage) toxicity study in rats (R31193, R31293 and R01994). In this study, MTD was identified at 25 mg/kg/day for males and 60 mg/kg/day for females. Both Division and CAC recommended sponsor to use doses of 7.5, 15 and 30 mg/kg/day in males and 15, 30 and 60 mg/kg/day in females. However, sponsor instead chose the doses of 5, 15, 30 and 60 mg/kg/day in males and 5, 15, 30, 60 and 120 mg/kg/day in females in the 2-year carcinogenicity study. In the current study, the high dose tested (60 mg/kg in males and 120 mg/kg in females) exceeded MTD since there were significantly increased mortality and histopathological changes in the stomach and kidney. Slightly lower (91-92%) in the body weight in the high dose group as compared to control was noted in both males and females. A significant increase in the mean gastrin level was seen in all treatment groups. There were no treatment related changes in the tumor incidence in males but in females the treatment produced malignant and benign carcinoid tumors in the stomach. The incidence of the carcinoid tumors (malignant and benign) in the stomach in females was 0, 0, 1, 3, 6, 5 and 7 in the control1, control2, 5, 15, 30, 60 and 120 mg/kg groups, respectively. The combined benign and malignant carcinoid tumors in the stomach were found to have positive linear trends using data from pooled control, 5, 15, 30, 60 and 120 mg/kg/day dose groups ($p<0.001$). Significant positivity is retained even after deleting 120 mg/kg/ day group; 60 and 120 mg/kg/day groups; and 30, 60 and 120 mg/ kg/day groups from comparisons. There was no significant heterogeneity found between the two control groups.

COVERSHEET FOR CARCINOGENICITY STUDY IN RATS

1. No. Of Studies: One

2. Name of Laboratory: [redacted]

3. Strain: Sprague-Dawley (SD/Tac) rats

4. No/sex/group: 70 males/group or 60 females/group

5. Doses (01, 02, L, M, H1, H2): 0, 0, 5, 15, 30 and 60 mg/kg/day (males) and 0, 0, 5, 15, 30, 60 and 120 mg/kg/day (females)

6. Basis for Dose Selection Stated: Yes

7. Interim Sacrifice: No

8. Total Duration (weeks): 104 weeks for both males and females.

9. Week/Site for First Tumor:

Chronological tumor data were not provided.

10. No. Alive at Termination:

Survival in Males

	con1	Con2	T1	T2	T3	T4
No. alive	15	6	17	8	3	8
% survival	21.4	8.6	24.3	11.4	4.3	11.4

Survival in Females

	con1	Con2	T1	T2	T3	T4	T5
No. alive	28	20	31	17	24	26	13
% survival	46.7	33.3	51.7	28.3	40	43.3	21.7

animals in each group: 70 males/group, 60 females/group,
Con1 and Con2 = control1 and control2,
For males, T1, T2, T3 and T4 = 5, 15, 30 and 60 mg/kg/day
For females, T1, T2, T3, T4 and T5 = 5, 15, 30, 60 and 120 mg/kg/day

The survival rates at the beginning of week 80 and end of week 90 were also summarized in tables on pages 20 and 21 in volume 1.52. These tables are attached below.

Male Survival Rates and Counts at the Beginning of Week 80 and End of Week 90, Study R00995

Time	Dose					
	0 mg/kg	0 mg/kg	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Week 80 (beginning)	73% (51/70)	64% (45/70)	74% (52/70)	61% (43/70)	40% (28/70)	30% (21/70)
Week 90 (end)	53% (37/70)	37% (26/70)	50% (35/70)	41% (29/70)	26% (18/70)	27% (19/70)

Note: Numerator is the number of animals alive in the given week and denominator is the total number of animals at the start of the study.

Female Survival Rates and Counts at the Beginning of Week 80 and End of Week 90, Study R01095

Time	Dose						
	0 mg/kg	0 mg/kg	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
Week 80 (beginning)	85% (51/60)	87% (52/60)	90% (54/60)	93% (56/60)	78% (47/60)	75% (45/60)	65% (39/60)
Week 90 (end)	65% (39/60)	63% (38/60)	77% (46/60)	63% (38/60)	67% (40/60)	63% (37/60)	50% (30/60)

Note: Numerator is the number of animals alive in the given week and denominator is the total number of animals at the start of the study.

11. Statistical Methods Used: The tumor data were analyzed using the prevalence method of Peto (Peto, R. et.al., Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiment in Long-term and short term screening assays for carcinogens: a critical appraisal. Geneva: WHO, pp 311-426, 1980) and life table analysis (death rate).

12. Attach Tumor and Non-tumor Data For Each Tissue: Tumor and non-tumor data attached in Appendix III.

Two Year Carcinogenicity Study of Rabeprazole Sodium in Rats (R00995 and R01095)

Testing Laboratories: [redacted]

Study Start and Completion Dates: January 23, 1995 and September 29, 1997

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulation and a quality assurance statement.

Animals: Males (178-262 g, 7-8 weeks)
Females (153-228 g, 8-9 weeks)
Sprague-Dawley (SD/Tac) rats

Methods: To determine the carcinogenic potential of rabeprazole, rats (70 males/group or 60 females/group) were treated with rabeprazole by oral gavage at 0, 0, 5, 15, 30 and 60 mg/kg/day (males) or 0, 0, 5, 15, 30, 60 and 120 mg/kg/day (females) for 2 years. The dose selection was based on findings from the 3 month oral (gavage) toxicity study in rats (R31193, R31293 and R01994). In this study, MTD was identified at 25 mg/kg/day for males and 60 mg/kg/day for females. The Division recommended sponsor to use 7.5, 15 and 30 mg/kg/day doses in males and 15, 30 and 60 mg/kg/day doses in females (see Division letter dated January 5, 1995) and CAC Executive Committee agreed with the Division recommendation (see CAC meeting minutes dated December 16, 1994). However, sponsor instead chose the doses of 5, 15, 30 and 60 mg/kg/day in males and 5, 15, 30, 60 and 120 mg/kg/day in females. In the current study, clinical signs of toxicity and mortality were observed daily. Body weights and food consumption were determined weekly. Ophthalmology examination was conducted before treatment and on treatment days 176, 358 and 540. Hematology and clinical chemistry were conducted at termination. Gastrin level was determined on the first day of treatment, at 3, 6, 12, 18 months and at termination. All animals were necropsied at termination and gross and histopathological examinations were conducted. The tissues examined histopathologically were listed in a table on page 2 in volume 1.53 and this table is attached below.

Tissue Preservation

The following tissues from each animal were preserved in 10% neutral buffered formalin:

Kidney	Ileum	Skeletal Muscle
Urinary Bladder	Cecum	Bone
Liver	Colon	Bone Marrow
Heart	Rectum	Adrenal
Aorta	Testis	Thyroid
Trachea	Epididymis	Parathyroid
Lung	Prostate	Pituitary
Spleen	Seminal Vesicle	Cerebrum
Lymph Node	Ovary	Cerebellum
Thymus	Uterus	Brain Stem
Salivary Gland	Cervix	Spinal Cord
Pancreas	Vagina	Sciatic Nerve
Tongue	Skin	Eye
Esophagus	Mammary Gland	
Stomach[a]	Harderian Gland	
Duodenum[a]		
Jejunum		

[a] Stomach (including duodenum) of terminal and moribund kill rats was fixed by inflating with and then immersing in zinc formalin. After fixation the stomach was trimmed, opened, washed, examined, and weighed. After 28 October 1996, the stomachs from early death animals were fixed by immersing in zinc formalin after opening and examining.

Plasma levels of the parent drug and its metabolites were determined at 0.5 and 24 hours after ~13, 26, 53 and 78 weeks in the satellite animals (3/sex/group). The tumor data were analyzed using the prevalence method of Peto (Peto, R. et.al., Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiment in Long-term and short term screening assays for carcinogens: a critical appraisal. Geneva: WHO, pp 311-426, 1980) and life table analysis (death rate).

Results:

1. Clinical Signs: Following treatment related clinical signs of toxicity were observed: salivation (at ≥15 mg/kg in males or ≥30 mg/kg in females), thinness (at ≥30 mg/kg in males or 15 and 120 mg/kg in females), soiling of the mouth and muzzle (at ≥30 mg/kg in females) and chromorhinorrhea, rales, labored respiration and rough hair coat (at 120 mg/kg in females).

2. Mortality: The survival rate at the end of the treatment period was 21.4%, 8.6%, 24.3%, 11.4%, 4.3% and 11.4% for males treated at 0, 0, 5, 15, 30 and 60 mg/kg or 46.7%, 33.3%, 51.7%, 28.3%, 40%, 43.3% and 21.7% for females treated at 0, 0, 5, 15, 30, 60 and 120 mg/kg, respectively. A significant increased trend in the mortality rate was detected in the combined control and treatment groups ($p<0.001$ for males and $p=0.006$ for females).

The intercurrent mortality (unscheduled deaths) was summarized in the following tables.

Mortality (Unscheduled Death) in Males

Weeks	con1	Con2	T1	T2	T3	T4
0-52	5	3	6	2	6	8
52-77	13	20	12	25	33	32
77-90	16	23	19	15	14	11
90-104	21	18	16	20	14	11
Total	55	64	53	62	67	62

Mortality (Unscheduled Death) in Females

Weeks	con1	Con2	T1	T2	T3	T4	T5
0-52	1	0	2	0	2	3	4
52-77	8	8	4	3	10	12	16
77-90	12	15	8	19	8	8	11
90-104	11	17	15	21	16	11	16
Total	32	40	29	43	36	34	47

animals in each group: 70 males/group, 60 females/group,
Con1 and Con2 = control1 and control2,
For males, T1, T2, T3 and T4 = 5, 15, 30 and 60 mg/kg/day
For females, T1, T2, T3, T4 and T5 = 5, 15, 30, 60 and 120 mg/kg/day

3. Body Weight: The initial and final body weights in the control groups were 222.2 and 556.3 for males or 187.6 and 425.2 for females. The terminal body weights in males treated at 5, 15, 30 and 60 mg/kg were 91, 92, 107 and 91% of the control, respectively. The terminal body weights in females treated at 5, 15, 30, 60 and 120 mg/kg were 98, 92, 100, 94 and 92% of the control, respectively. The body weight information is summarized in the following tables.