DATA EVALUATION REPORT

AE F122006
MRID 44973803
STUDY TYPE: CHRONIC TOXICITY/ONCOGENICITY ORAL STUDY - RAT
OPPTS 870.4300 [§83-5]

Prepared for

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U.S. Environmental Protection Agency
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Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/oncogenicity feeding- rat [OPPTS 870.4300 (§83-5)]

DP BARCODE: D253998
P.C. CODE: 999999

SUBMISSION CODE: S558007
TOX. CHEM. NO.: none

TEST MATERIAL (PURITY): AE F122006 (Hoe 122006) (98.7% a.i.)

SYNONYMS: none reported

CITATION: Higgs, P. 1999. Rat dietary combined chronic toxicity and oncogenicity study AE F122006 (Hoe 122006) Code: AE F122006 001C990002. AgrEvo UK Limited Toxicology, Chesterford Park, Saffron Walden, Essex CB10 XL, England. Laboratory Report No. TOX/99/252-71, October 8, 1999. MRID 44973803. Unpublished.

SPONSOR: AgrEvo USA Company, Little Falls Centre One, 2711 Centerville Road, Wilmington, DE 19808

EXECUTIVE SUMMARY:

In a chronic toxicity/oncogenicity study (MRID 44973803), AE F122006 (98.7%, Lot #AE F122006 1C99 0002) was administered to groups of 70 male and 70 female Sprague-Dawley CRL:CD (BR) rats at dietary concentrations of 0, 20, 200, 2000, or 4000 ppm (0, 0.8, 8, 84, and 171 mg/kg/day, respectively, for males and 0, 1.1, 12, 118, and 249 mg/kg/day, respectively, for females) for up to 24 months. Twenty males and 20 females were sacrificed at 12 months for interim evaluation.

No treatment-related or toxicologically significant effects were observed on mortality, hematology, clinical chemistry parameters, organ weights, or incidences of gross lesions in either sex. The only clinical sign related to treatment with the test material was urogenital staining observed in a significantly greater number of male rats and for a greater number of days in females administered the 4000-ppm diet. Male rats administered the 4000-ppm diet weighed up to 8% ($p<0.05$) less than controls during the first year of treatment, weighed only 2% less than controls at the study termination, gained 19% less weight than controls during the first week of treatment, and gained only 2% less weight than controls over the entire study. Females in the

4000-ppm group weighed up to 14% ($p<0.05$) less than controls during the first 18 months, weighed 5% less at study termination, gained 38% less weight during the first week, and gained 8% less over the entire study. The reduction in food consumption in males during the first week (18%, $p<0.05$) accounted for the reduced body weight gain, but reduced food consumption by females (10%, $p<0.05$) during the first week of treatment only partially accounted for the reduced body weight gain. At 4000 ppm, food efficiency was reduced by 31% in females but was similar in treated and control male groups.

Treatment-related adaptive microscopic findings were observed in male rats; minimal centrilobular hepatocyte hypertrophy occurred in 1/20, 2/20, 0/20, 5/20 (N.S.), and 15/20 ($p<0.01$) males administered the 0,- 20-, 200-, 2000-, or 4000-ppm diets for 12 months and in 0/50, 0/50, 1/50, 1/50, and 13/50($p<0.01$) males, respectively, in the main study. In addition, proteinaceous plugs in the urinary bladder occurred in 1/50, 2/50, 2/50, 4/50, and 7/50 ($p<0.05$) males in the main study. The only treatment-related microscopic finding in female rats was a greater average severity grade (2.29) for progressive nephropathy in the 4000-ppm group compared with that of controls (1.38).

The lowest-observed-adverse-effect level (LOAEL) was 4000 ppm (171 mg/kg/day for males and 249 mg/kg/day for females) for male and female rats based on transient decreases in body weight and body weight gain for both sexes, proteinaceous plugs in the urinary bladder of males, and increased severity of progressive nephropathy in females. The corresponding no-observed-adverse-effect level (NOAEL) was 2000 ppm (84 mg/kg/day for males and 118 mg/kg/day for females).

At the doses tested, administration of AE F122006 did not cause an increase in the incidence of neoplasms at any site. The overall tumor rate was similar between treated and control animals of both sexes. It is possible that the animals could have tolerated a higher dose, because, after the first week of treatment, body weight gain was only slightly reduced in both sexes. Nevertheless, there is no reason to repeat the study using higher doses.

This chronic toxicity /oncogenicity study in the rat is **Acceptable/Guideline** and, does satisfy the guideline requirement for a chronic toxicity/oncogenicity oral study in the rat [OPPTS 870.4300 (§83-5)] . There were no noteworthy deficiencies in the conduct of this study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: AE F122006 (Hoe 122006)

   Description: cream powder
   Lot/Batch #: AE F122006 00 1C99 0002

Purity: 98.7% a.i.
Stability of compound: duration of the study.
CAS #: not reported
Structure: not available

2. Vehicle and/or positive control
The test material was administered in the diet (Modified SQC Expanded Rat and Mouse Maintenance Diet No. 1); no positive control was used in this study

3. Test animals
Species: rat
Strain: Sprague-Dawley CRL:CD (IGS) (BR)
Age and weight at study initiation: ~40 days old; males: 134 - 211 g; females: 117 - 182 g
Source: Charles River UK, Ltd., Margate, Kent, UK
Housing: Housed in groups of five of the same sex in suspended polycarbonate cages with wire tops, grid floors, and solid sides.
Diet: Modified SQC Expanded Rat and Mouse Maintenance Diet No. 1 (Special Diet Services, Ltd., Stepfield, Witham, Essex, UK), *ad libitum*
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 19-23 °C
Humidity: 45-65%
Air changes: not reported
Photoperiod: 12 hours light/12 hours dark
Acclimation period: 15 days

B. STUDY DESIGN

1. In life dates

Start: November 14, 1996 end: Nov. 13-27, 1998

2. Animal assignment

Animals were randomly assigned to the test groups in Table 1 based on body weights; each group had similar initial mean body weights and weight distributions.

TABLE 1: Study design							
Test Group	Conc. in Diet (ppm)	Dose to animal (mg/kg/day)		Main Study 24 months		Interim Sacrifice 12 months	
		male	female	male	female	male	female
1 – Control	0	0	0	50	50	20	20
2	20	0.8	1.1	50	50	20	20
3	200	8	12	50	50	20	20
4	2000	84	118	50	50	20	20
5	4000	171	249	50	50	20	20

Data taken from page 15 and 24, MRID 44973803.

3. Dose selection rationale

Dose selection was based on a 90-day toxicity study in rats. Details were not presented in this report.

4. Diet preparation and analysis

Diets for the two highest formulations were prepared weekly by mixing appropriate amounts of test substance with diet (Modified SQC Expanded Rat and Mouse Maintenance Diet No. 1) in two identical batches. The diets were prepared using a grinder and Kenwood mixer followed by mixing in a Turbula mixer for 30 minutes. Other dietary formulations were prepared by serial dilution. During the first 4 weeks, the diets were offered to the rats for a 3- or 4-day period, with one portion kept frozen until used. In addition, over the Christmas holidays, batches were prepared in advance for a 4-week period and stored frozen until used. Homogeneity was tested on all dietary formulations before study initiation and at week 65. Stability was tested before study initiation on all dietary formulations stored at room temperature for 1, 2, 4, 8, and 15 days. During the study, samples of treated food were analyzed for concentration at irregular intervals throughout the study.

Results

Homogeneity Analysis:

The measured concentrations of AE F122006 in samples taken from the top, middle, and bottom of the mixer were within 6% of the target concentrations.

Stability Analysis:

The concentrations of AE F122006 in the 20- and 200-ppm dietary samples showed an apparent decline of 13% and 11%, respectively, after storage for 8 days and analysis after a single acetone extraction when compared with the day 0 concentrations. After double acetone extractions, the concentrations were within 6% of the day 0 concentrations after storage up to 15 days at room temperature.

Concentration Analysis: The mean concentrations of AE F122006 in all samples were within 10% of target concentration.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics

Body weight, food consumption, and organ weight data: Bartlett's test for homogeneity followed by one-way-analysis of variance (ANOVA) if Bartlett's test was not significant, then Dunnett's test was used for comparison of treated groups with controls if ANOVA was significant. If Bartlett's test indicated heterogeneity, a modified test was used for pairwise comparison.

Hematology and clinical chemistry data: Bartlett's test was used to determine homogeneity/heterogeneity of variance. Log transformation was used to remove heterogeneity. ANOVA was used on untransformed homogeneous or log transformed homogeneous data followed by Student's t-test for pairwise comparisons. If log transformation did not remove heterogeneity, Kruskal-Wallis test was used for pairwise comparisons.

Nonneoplastic findings: The method of Peto (1980) was used to analyze incidence data involving lesions occurring in at least three animals and taking into account whether the lesion was lethal or nonlethal. The incidence within each severity grade was also analyzed.

Neoplastic findings: The method of Peto (1980) was used for analyzing incidence data involving lesions occurring in at least three animals, taking into account whether the lesion was lethal or nonlethal and differences in survival. Exact tests (not otherwise specified) were used when the incidences were low.

Statistical significance was indicated by $p<0.05$.

C. METHODS

1. Observations

Animals were inspected daily on weekdays for signs of toxicity (abnormal behavior, neuromuscular coordination and physical appearance) and mortality. Detailed observations with palpation were conducted once a week before weighing.

2 Body weight

Animals were weighed at the start of treatment, weekly for 14 weeks, biweekly thereafter, and at necropsy.

3. Food consumption and compound intake

Food consumption for each animal was determined weekly for 13 weeks and at 4-week intervals thereafter. Mean daily diet consumption was calculated as g food/animal/day. Food conversion (efficiency) was calculated as follows: ((weight gain in g/food consumption in g per unit time) × 100). Mean compound intake (mg/kg/day) values were calculated from the consumption and body weight data.

4. Water consumption

Water consumption for the number of cages containing a total of 20 rats per sex per group was measured over a 5-day period during weeks 9, 17, 33, and 49 of treatment and was calculated as g/animal/day.

5. Ophthalmoscopic examination

Eyes of all animals were examined before study initiation, and the eyes of animals in the control and 4000-ppm groups were examined before interim and terminal sacrifices.

6. Blood was collected from the retro-orbital sinus of ten animals per sex per dose group at 3, 6, 12, 18, and 24 months for hematology and clinical analysis. Before collecting blood, the animals were anesthetized with ether during the first year and isoflurane during the second year . The study author did not indicate whether the animals were fasted before collection of blood. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Large unstained cells
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Platelet count*	X	Mean corpusc. volume (MCV)
X	Blood clotting measurements* (Thromboplastin time)	X	Reticulocyte count
X	Activated partial thromboplastin time (Clotting time)		
X	(Prothrombin time)		

* Required for chronic toxicity/oncogenicity based on Subdivision F Guidelines

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Total Globulins
X	Sodium*	X	A/G Ratio
		X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein*
X	Alkaline phosphatase (ALK)		Triglycerides
	Cholinesterase (ChE)		
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase* (SGPT)		
X	Serum aspartate amino-transferase* (SGOT)		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for chronic toxicity/oncogenicity studies based on Subdivision F Guidelines

6. Urinalysis

Urine was collected overnight from ten animals/sex/dose group at 3, 6, 12, 18, and 24 months. Food but not water was removed during collection. The CHECKED (X) parameters were examined. In addition, the urine was examined for bacteria, red blood cells, epithelial cells, phosphate crystals, urate crystals, casts, white blood cells, sperm, and spun deposit color.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

*Required for chronic toxicity/oncogenicity studies based on Subdivision F Guidelines

7. Sacrifice and pathology

All animals that died before study termination and those sacrificed *in extremis* or on schedule by exsanguination under ether anesthesia were subjected to gross pathological examination. The CHECKED (X) tissues from all animals were collected and examined microscopically. In addition, the [XX] organs were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*		
X	Ileum*				GLANDULAR
X	Cecum*		UROGENITAL	XX	Adrenal gland*
X	Colon*	XX	Kidneys*+	X	Lacrimal gland
X	Rectum*	X	Urinary bladder*	X	Harderian gland
XX	Liver*+	XX	Testes*+	X	Mammary gland*
X	Bile duce	XX	Epididymides	X	Parathyroids*
X	Pancreas*	X	Prostate	X	Thyroids*
		X	Seminal vesicle		
	RESPIRATORY	XX	Ovaries*		OTHER
X	Trachea*	X	Oviduct	X	Bone*
X	Lung*	X	Uterus*	X	Skeletal muscle*
	Nose	X	Vagina	X	Skin*
	Pharynx			X	Diaphragm
	Larynx			X	All gross lesions and masses*

*Required for chronic toxicity/oncogenicity studies based on Subdivision F Guidelines.
+Organ weight required in chronic toxicity/oncogenicity studies.

II. RESULTS

A. Observations

1. Toxicity

A total of 21/70 ($p<0.05$, Fisher exact test calculated by the reviewer) male rats receiving the 4000-ppm diet had evidence of urogenital staining for an average of 99 days compared with only 10/70 controls for an average of 15.3 days. A total of 10/70 (N.S.) female rats receiving the 4000-ppm diet had evidence of urogenital staining for an average of 68.1 days compared with 6/70 controls for an average of only 9.3 days. The remaining clinical signs occurred with a similar frequency in both sexes receiving the test material and the corresponding controls.

2. Mortality

No treatment-related effects were observed on the survival of rats receiving any dose of the test material. At least 80% of males and 74% of females in each group survived to 18 months (78 weeks). At 104 weeks, survival was 54, 46, 52, 62, and 66% for males and 34, 44, 46, 32, and 38% for females receiving dietary concentrations of 0, 20, 200, 2000, and 4000 ppm.

B. Body weight

Selected mean body weights and body weight gain data are presented in Table 2. Male rats receiving the 4000-ppm diet weighed significantly less (up to 8%, $p<0.05$) than controls from the first week of treatment to the end of the first year; during the second year, body weights were significantly different from controls at sporadic time points, but was similar to that of controls at the end of the study. Males receiving the 2000-ppm diet weighed significantly less (up to -6%, $p<0.05$) than controls from day 22 to day 78 (week 3-11); thereafter body weights were similar to that of controls. Body weights of the 20- and 200-ppm groups were similar to that of controls throughout the study. Male rats receiving the 4000-ppm diet gained 19% less weight than controls during the first week of treatment, gained only 8% less over the first year, but gained 58% more weight than controls during the second year resulting in an overall weight gain similar to that of controls. Males in the 2000-ppm group gained almost twice as much weight as controls during the second year of treatment. Weight gain in the 20- and 200-ppm groups was similar to that of controls.

Females receiving the 4000-ppm diet weighed significantly ($p<0.05$) less than controls during the first 18 months of the study, up to 8% less during the first year and up to 14% ($p<0.05$) less than controls during the next 6 months. Females in the remaining treatment groups had body weights similar to those of controls. Females in the 4000-ppm group gained 38% less weight than controls during the first week of treatment, 14% less during the first year, 4% more during the second year, and only 8% less over the entire study. Weight gain in the remaining groups was similar to that of controls.

TABLE 2. Selected mean body weights and body weight gain in male and female rats receiving AE F122006 for up to 104 weeks.

Day of Study	Males					Females				
	0	20	200	2000	4000	0	20	200	2000	4000
Body weights (g)										
1	175	172	173	173	175	150	150	148	150	150
8	229	227	227	224	219* (96)[a]	176	177	174	176	166* (94)
92	512	501	501	492	482* (94)	296	297	292	291	277* (94)
183	617	605	602	595	583* (94)	334	338	333	327	312* (93)
365	729	727	717	712	686* (94)	410	426	422	405	379* (92)
547	798	803	777	774	747 (94)	491	511	486	471	424* (86)
729	781	822	791	808	768 (98)	509	535	513	495	482 (95)
Body weight gain (g) [b]										
1-8	54	55	54	51	44 (81)	26	27	26	26	16 (62)
1-92	337	329	328	319	307 (91)	146	147	144	141	127 (87)
1-365	554	555	544	539	511 (92)	260	276	274	255	229 (88)
365-729	52	95	74	96	82 (158)	99	109	91	90	103 (104)
1-729	606	650	618	635	593 (98)	359	385	365	345	332 (92)

Data taken from page 23 and Table 1.7 (pp. 55-64), MRID 44973803.
[a]Numbers in parentheses are percent of control, calculated by the reviewer.
[b]Body weight gain calculated by the reviewer except for day 1-729/
*$p<0.05$, statistically significant, treated group compared with the control.

C. Food consumption and compound intake

1. Food consumption

At the 4000-ppm dietary level, male rats consumed 18% ($p<0.05$) less food than controls and females consumed 10% ($p<0.05$) less food than controls during the first week of treatment; food consumption for both sexes in the 4000-ppm group was similar to that of controls for the remainder of the study except for a few sporadic time points. Except for a few sporadic time points, food consumption by males and females in the other treatment groups also was similar to that of the controls.

2. Compound consumption

Compound intake is summarized in Table 1.

3. Food efficiency

Food conversion (efficiency) values for male and female rats were not affected by treatment with any dose of the test material or at any time during the first 13 weeks except for the first week of the study when food efficiency was reduced by 31% in females administered the 4000-ppm diet. Statistical significance was not reported.

4. Water consumption

No differences were observed between the amount of water consumed by male rats receiving any dose of the test material and the control group. Females receiving the 4000-ppm diet consumed 21-27% ($p<0.05$) more water than controls during weeks 33 and 49. Otherwise, water consumption by all groups of treated females was similar to that of controls.

D. Ophthalmoscopic examination

The eyes were examined only in the 4000-ppm and control groups. At study termination, 13/37 (35%, $p=0.06$) treated male rats had evidence of lens opacity compared with 5/32 (16%) in controls. There was no difference in the incidence of lens abnormalities in treated females compared with controls.

E. Blood work

1. Hematology

The total white cell count (WBC) was consistently increased (6-16%, N.S.) in 4000-ppm group males at each time point, and the differential count showed consistent increases in the lymphocyte (111-158%) and monocyte (150-200%, except at 24 months) counts and a consistent decrease in the neutrophil count (53-77% of the control counts, except for 12 months). Statistical significance ($p<0.05$) was attained at 3 and 18 months for neutrophil counts, 18 months for lymphocyte counts, and 3, 6, 12, and 18 months for monocyte counts. The total and differential WBC were similar in treated and control female rats.

2. Clinical chemistry

The 4000-ppm group male rats had significantly ($p<0.01$ or <0.05) increased serum alkaline phosphatase activity (27-37%) and urea levels (11-15%) during the first 12 months, and increased creatinine levels (8-16%) at all time points. Urine Creatinine levels were also significantly ($p<0.01$) increased in 2000-ppm group males by 10-16% compared with the control levels at 12, 18, and 24 months. However, a clear dose-related trend was not observed for these parameters; these changes also did not become progressively more severe with increased treatment time. Other changes in 4000-ppm group males were transient and/or too small to be considered

toxicologically significant or treatment related. No consistent statistically significant, dose-related, or time-related changes were observed for any parameters in females receiving any dose of the test material.

F. Urinalysis

The incidence of male rats with ketones in their urine was increased compared with that of controls, particularly at the two highest doses (Table 3). In 4000-ppm group males, the incidence was 90-100% at 3, 6, and 12 months, 90% in 2000-ppm group males at 3 and 6 months, and 20-30% in 200-ppm group males at 3 and 6 months compared with 0-10% for controls. The incidence of this finding decreased with increased treatment time; only 20% of 2000- and 4000-ppm group males and none of the 200-ppm group males had ketones in their urine at the end of the study. The urine of male rats receiving the 2000- and 4000-ppm diets was significantly more acidic than that of controls (pH 6 vs pH 7 for controls ($p<0.01$) at 3, 18, and 24 months; the lack of consistency with dose and time suggests that this finding is not treatment-related. No other treatment-related or notable changes in urinalysis parameters were observed in male or female rats receiving any dose of the test material.

TABLE 3. Incidence of male rats with ketones in urine

Time of Urine Sampling (Month)	Dietary Concentration (ppm)				
	0	20	200	2000	4000
No. Animals/group	10	10	10	10	10
3	1	0	3	9	10
6	0	0	2	9	10
12	0	1	0	5	9
18	0	0	0	2	5
24	0	0	0	2	2

Data taken from Table 2.5, pages 132-161, MRID 44973803.

G. Sacrifice and pathology

1. Organ weight

Except for the absolute kidney weight and relative liver weight in male rats, no statistically significant changes were observed for absolute organ weights of either sex or relative organ weights for female rats at interim sacrifice. The absolute kidney weight of 2000-ppm group males was significantly decreased by 8 % ($p<0.01$) at interim sacrifice, but the 8% decrease in 4000-ppm group males did not attain statistical significance. The absolute liver weights in males at 2000 and 4000 ppm were increased (N.S.) by 9 and 11%, respectively, and the relative liver weights were

significantly increased by 8% ($p<0.05$) and 16% ($p<0.01$), respectively compared with that of controls.

At study termination, absolute kidney weights were significantly decreased in 2000- and 4000-ppm group males by 10% ($p<0.05$) and 12% ($p<0.01$), respectively, compared with controls. Relative kidney weights were also significantly decreased by 13% ($p<0.05$) and 9% (<0.05), respectively. The absolute liver weight of 4000-ppm group males was similar to that of controls at study termination, but the relative liver weight was significantly increased by 8% ($p<0.05$). Except for the decrease in absolute kidney weight of 2000-ppm group female rats (-20%, $p<0.05$), no statistically significant changes were observed in absolute or relative organ weights of female rats receiving any dose of the test material.

2. Gross pathology

No treatment-related gross lesions were observed in male or female rats receiving any dose of the test material for up to 12 or 24 months.

3. Microscopic pathology

a. Non-neoplastic

Notable nonneoplastic lesions are presented in Table 4. In rats sacrificed at 12 months, minimal centrilobular hepatocyte hypertrophy was observed in 75% ($p<0.01$) of males receiving the 4000-ppm diet and in 25% ($p=0.09$) of males receiving the 2000-ppm diet compared with 5% of controls. No treatment-related microscopic lesions occurred in females receiving any dose of the test material for 12 months.

In main study rats receiving the test material for up to 24 months, centrilobular hepatocyte hypertrophy was observed in 26% ($p<0.01$) of males receiving the 4000-ppm diet compared with none of the controls and 20-ppm group and only 2% each in the 200- and 2000-ppm groups. The lesions were graded slight in one rat and minimal in the remaining 4000-ppm group male rats. Male rats in the 4000-ppm group also had a significantly higher incidence of urinary bladders with proteinaceous plugs (14%, $p<0.05$) compared with only 2% of the controls. In addition, 8%, 4%, and 4% of 2000-, 200-, and 20-ppm group males, respectively, also had this lesion, but the incidence did not attain statistical significance. In main study females, the severity of progressive nephropathy at the 4000-ppm dose level was noticeably increased compared with that of controls. In addition, the incidence of pelvic epithelial hyperplasia was significantly increased (56-72%, $p<0.01$) at all doses compared with a 30% incidence in the controls. The increased incidence of this lesion did not show a dose-related trend and no clear increase in the severity, suggesting that it is unlikely to be related to treatment with the test material.

TABLE 4. Notable nonneoplastic lesions in male and female rats fed AE F122006 for up to 104 weeks					
Organ/lesion	Dietary Concentration (ppm)				
	0	20	200	2000	4000
Males – 12 Months					
Liver (centrilobular) [No. animals]	20	20	20	20	20
Hepatocyte hypertrophy	1 (1.00)[a]	2 (1.00)	0 (1.00)	5 (1.00)	15** (1.00)
Males – Main Study					
Liver (centrilobular) [No. animals]	50	50	50	50	50
Hepatocyte Hypertrophy	0	0	1 (1.00)	1 (1.00)	13** (1.08)
Urinary Bladder [No. animals]	50	50	49	50	50
Proteinaceous plug	1	2	2	4	7*
Females – Main Study					
Kidney [No. animals]	50	50	49	50	50
Progressive nephropathy	25 (1.38)	22 (1.50)	23 (1.48)	17 (1.29)	31 (2.29)
Pelvic epithelial hyperplasia	15 (1.47)	36** (1.19)	30** (1.23)	28** (1.32)	35** (1.66)

Data taken from Tables 4.3 (pp. 239-264) and 4.4 (pp. 265-317), MRID 44973803.
[a]Numbers in parentheses are average severity grade: 1 = minimal, 2 = slight, 3 = moderate, 4 = severe, and 5 = very severe.
*$p<0.05$, **$p<0.01$, statistically significant, treated groups compared with the control group using Fisher Exact Test calculated by the reviewer.

b. Neoplastic

No treatment-related neoplastic lesions were observed in either male or female rats receiving any dose of the test material. Common neoplasms seen at all dose levels including controls included pituitary adenomas (pars distalis) in 44-58% of males and 68-84% of females and mammary fibroadenoma in 44-62% of females in the main study (see Attachment).

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS

The investigators concluded that AE F122006 was not oncogenic in the rat and that the no-observed-effect level (NOEL) was 200 ppm.

B. REVIEWER'S DISCUSSION/CONCLUSIONS

Administration of AE F122006 caused no increase in mortality, and sufficient animals were alive in all groups at 18 months and at study termination to assess the effect of the test material on late-developing lesions. The only clinical sign possibly associated with administration of AE F122006 was urogenital staining in male and female rats receiving the 4000-ppm diet. Staining was observed in a significantly greater number of male rats and for a markedly greater number of days in female rats. Body weights were reduced in

both male and female rats at the 4000-ppm dietary level. The differences between the treated groups and controls did not exceed 8% for males and 14% for females and the differences occurred primarily during the first year of treatment for males and during the first 18 months for females. The transient nature of the effect on body weights was exhibited by the lack of a significant difference in body weight of both sexes at study termination compared with the weight of controls. Body weights of 2000-ppm group males were slightly but significantly affected for a few weeks during the early part of the study. Body weight gain and food consumption by male rats were affected to approximately the same degree during the first week of treatment; consequently, food efficiency was similar in treated male rats and the controls. Food consumption was only slightly affected in females; consequently, the food efficiency value for the first week of treatment, but not later times, was much lower than that of controls. Water consumption by treated rats was generally similar to that of controls, except for the 21-27% increases observed at two time points in 4000-ppm group females. The reviewer could not relate the increased water consumption with any pathologic condition.

The only noteworthy hematologic changes were the slight increases in total WBC in 4000-ppm group males and concomitant changes in selected differential WBC counts. The magnitude of the changes in WBC and differential counts were not toxicologically significant and associated pathologic changes were not apparent. Serum alkaline phosphatase activity was significantly elevated during the first year of treatment. Increased serum alkaline phosphatase is associated with biliary disease of the liver, but the bile duct was not affected by administration of the test material. Serum creatinine levels were slightly elevated throughout the study in 4000-ppm group males. The number of males with ketone in their urine was significantly increased at 2000 and 4000 ppm; this observation was transient at both doses and was no longer apparent in the 2000-ppm group at 18 and 24 months and in the 4000-ppm group at 24 month. Increases in serum creatinine and urine ketone are known to be associated with starvation and muscle loss and increased serum creatinine may be associated with kidney damage; however, the reviewer found no evidence of starvation or treatment-related kidney damage in male rats. Therefore, the toxicologic significance of both observations is unknown. The pH of urine in male rats was more acidic at some time points, but there was no consistency with dose and duration of treatment and the values were within the normal range.

Organ weights in females were not affected by treatment with any dose of the test material. The statistically significant decrease in absolute kidney weight in the 2000-ppm group females was not considered treatment related, because no significant difference was observed at the 4000-ppm dose level. Relative liver weight in 2000- and 4000-ppm group males was significantly increased at interim sacrifice, but not at study termination. The transient increase in relative liver weight was probably the result of the slight increase in absolute liver weight (N.S.) and the slight decrease in absolute body weight. Absolute and relative kidney weights were significantly decreased in 2000- and 4000-ppm group males at study termination; there were no pathological correlates to account for the decreased kidney weight. Therefore, the change in kidney weight in male rats is not considered toxicologically significant. The study author considered the increased

relative liver weight in males at 52 weeks, the decreased absolute and relative kidney weights in main study males, along with the presence of ketones in the urine of males at 2000 ppm to be treatment related and was used as the basis for establishing the lowest effect level. The reviewer agrees that these effects are likely treatment related, but they are not toxicologically significant and are not used by the reviewer for setting the adverse effect level.

No gross findings were related to treatment with the test material. Treatment-related microscopic findings in rats killed at interim sacrifice included minimal centrilobular hepatocyte hypertrophy in 2000- and 4000-ppm group males. In main study male rats, the incidence of centrilobular hepatocyte hypertrophy at 2000 ppm and 4000 ppm were reduced compared to the incidence observed at 12 months. In addition, severity of the lesion in main study animals did not increase with continued treatment with the test material. Therefore, it is appears that centrilobular hypertrophy was an adaptive rather than an adverse response to treatment with the test material and it was partially reversed with continued treatment. Further, the minimal severity throughout the study also suggests that the lesion was not adverse. Male rats also had a dose-related increase in the incidence of proteinaceous plugs in the urinary bladder that attained statistical significance at 4000 ppm. Females in the 4000-ppm main study group had an increase in the severity of progressive nephropathy compared with the controls; the incidence was not significantly increased. All dose groups of females also had an increased incidence of pelvic epithelial hyperplasia; however, a dose-related trend was not apparent, the severity was not notably increased, and the background was high for the controls indicating that this lesion was not treatment related.

In conclusion, the LOAEL was 4000 ppm (171 mg/kg/day for males and 249 mg/kg/day for females) for male and female rats based on transient decreases in body weights and body weight gain in both sexes, proteinaceous plugs in the urinary bladder of males and increased severity of progressive nephropathy in females. The corresponding no-observed-adverse-effect level (NOAEL) was 2000 ppm.

No treatment-related neoplasms developed in either male or female rats administered the test material. Based on the slight decrease in body weight gain after the first week of treatment, the animals could have tolerated a higher dose. Because treatment-related effects were identified at the two highest doses (not considered toxicologically significant at the 2000-ppm dose level), the reviewer does not consider it necessary to repeat this study using higher doses.

C. STUDY DEFICIENCIES

There were no noteworthy deficiencies in the conduct of this study.

ATTACHMENT-Neoplastic Incidence Table

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		24	26	28	22	25	25	19	31	17	33
Adrenal cortex											
CORTICAL TUMOURS											
absent		24	26	28	21	25	25	19	31	17	33
ADRENAL CORTICAL ADENOMA	b	0	0	0	1	0	0	0	0	0	0
Adrenal medulla											
MEDULLARY TUMOUR											
absent		18	20	23	18	19	21	17	25	15	26
PHAEOCHROMOCYTOMA	b	5	3	4	3	4	2	2	6	1	7
MALIGNANT PHAEOCHROMOCYTOMA	m	1	3	0	1	0	1	0	0	1	0
PARAGANGLIOMA	b	0	0	0	0	0	1	0	0	0	0
Brain											
CNS NEOPLASIA											
absent		24	26	27	22	24	25	19	30	16	32
ASTROCYTOMA	m	0	0	1	0	0	0	0	0	1	0
OLIGODENDROGLIOMA	m	0	0	0	0	1	0	0	0	0	0
MENINGIOMA	m	0	0	0	0	0	0	0	1	0	1
Haemopoietic system											
LYMPHOMATOUS TUMOUR											
absent		23	26	27	22	24	25	18	31	16	32
MALIGNANT LYMPHOMA	m	1	0	1	0	1	0	1	0	1	1
MYELOCYTIC TUMOUR											
absent		24	26	27	22	24	25	18	31	17	33
GRANULOCYTIC LEUKAEMIA	m	0	0	1	0	1	0	1	0	0	0
HISTIOCYTIC TUMOUR											
absent		24	25	28	22	23	25	17	31	17	32
HISTIOCYTIC SARCOMA	m	0	0	0	0	2	0	2	0	0	0
MONOCYTIC LEUKAEMIA	m	0	1	0	0	0	0	0	0	0	1
ARBITRARY PRIMARY, SECONDARIES ONLY PRESENT											
absent		24	26	27	22	25	25	19	31	17	33
CARCINOMA OF UNKNOWN ORIGIN	m	0	0	1	0	0	0	0	0	0	0
Heart											
CARDIAC TUMOURS											
absent		24	26	27	22	25	24	19	30	17	33
CARDIAC SCHWANNOMA	b	0	0	0	0	0	0	0	1	0	0
ATRIOCAVAL MESOTHELIOMA	m	0	0	1	0	0	1	0	0	0	0
Jejunum											
SMOOTH MUSCLE TUMOURS											
absent		24	26	28	22	24	25	19	31	16	33
LEIOMYOSARCOMA	m	0	0	0	0	0	0	0	0	1	0

Key : D = decedent T = terminal kill b = benign m = malignant
Pathologist: J P Finn

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		24	26	28	22	25	25	19	31	17	33
Joint											
JOINT TUMOUR											
absent		24	25	28	22	25	25	19	31	17	33
SYNOVIAL SARCOMA	m	0	1	0	0	0	0	0	0	0	0
Kidney											
TUMOUR CONNECTIVE TISSUE											
absent		24	26	28	22	25	24	19	31	17	33
LIPOMA	b	0	0	0	0	0	1	0	0	0	0
TUMOUR EPITHELIAL											
absent		24	24	28	22	25	25	19	31	17	33
RENAL ADENOMA	b	0	2	0	0	0	0	0	0	0	0
Liver											
HEPATOCELLULAR TUMOURS											
absent		24	26	28	19	24	24	19	31	16	33
one HEPATOCELLULAR ADENOMA	b	0	0	0	1	1	1	0	0	1	0
one HEPATOCELLULAR CARCINOMA	m	0	0	0	2	0	0	0	0	0	0
Lung											
PULMONARY TUMOURS											
absent		24	26	28	22	25	24	19	31	17	33
one PULMONARY CARCINOMA	m	0	0	0	0	0	1	0	0	0	0
Lymph node, mesenteric											
Vascular tumour											
absent		24	26	27	22	25	24	19	30	17	33
HAEMANGIOMA	b	0	0	0	0	0	1	0	1	0	0
LYMPHANGIOMA	b	0	0	1	0	0	0	0	0	0	0
Pancreas											
absent		21	26	26	21	25	22	18	27	17	31
ISLET CELL ADENOMA	b	3	0	2	1	0	3	0	4	0	2
PANCREATIC ACINAR TUMOURS											
absent		24	26	28	21	25	25	18	31	17	33
EXOCRINE ADENOMA	b	0	0	0	1	0	0	0	0	0	0
Parathyroid											
TUMOUR											
absent		24	25	25	22	22	25	18	30	16	30
ADENOMA	b	0	0	0	0	0	0	0	0	0	1

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		24	26	28	22	25	25	19	31	17	33
Pituitary											
PITUITARY TUMOUR											
absent		6	14	13	8	13	13	11	10	8	18
PARS DISTALIS ADENOMA	b	17	11	14	14	11	12	8	21	8	14
PARS INTERMEDIA ADENOMA	b	1	0	1	0	0	0	0	0	1	1
Prostate											
PROSTATIC TUMOURS											
absent		24	26	28	22	24	25	19	31	15	33
ADENOCARCINOMA	m	0	0	0	0	0	0	0	0	2	0
Seminal vesicle											
TUMOUR											
absent		24	26	28	22	23	25	19	31	17	33
ADENOCARCINOMA	m	0	0	0	0	1	0	0	0	0	0
Skin											
EPITHELIAL SKIN TUMOURS											
absent		22	22	27	18	22	19	17	23	17	28
one PAPILLOMA	b	1	0	1	1	0	1	0	0	0	0
one KERATOACANTHOMA	b	0	3	0	2	2	4	1	5	0	3
two KERATOACANTHOMAS	b	0	0	0	0	0	0	0	0	0	1
four KERATOACANTHOMAS	b	0	0	0	0	0	0	0	1	0	0
one SQUAMOUS CELL CARCINOMA	m	2	1	0	0	0	1	1	1	0	1
one BASAL CELL TUMOUR	b	0	0	0	1	0	0	0	1	0	0
one CARCINOMA, UNDIFFERENTIATED	m	0	0	0	0	1	0	0	0	0	0
CONNECTIVE TISSUE SKIN TUMOUR											
absent		21	21	23	11	19	21	17	25	15	23
one FIBROMA	b	1	2	1	4	2	3	1	4	0	8
two FIBROMAS	b	0	0	1	4	0	1	0	1	0	2
one FIBROSARCOMA	m	2	1	2	0	4	0	0	0	1	0
two FIBROSARCOMAS	m	0	0	1	0	0	0	0	0	1	0
one SARCOMA	m	0	0	1	0	0	0	1	0	0	0
one LIPOMA	b	1	2	0	2	0	0	0	0	0	0
one OSTEOGENIC SARCOMA	m	0	0	0	1	0	0	0	0	0	0
one AMELANOTIC MELANOMA	b	0	0	0	0	0	0	0	1	0	0
Spinal cord, cervical											
CNS TUMOURS											
absent		24	26	28	22	25	25	19	31	16	33
ASTROCYTOMA	m	0	0	0	0	0	0	0	0	1	0
Spleen											
SPLENIC NEOPLASIA											
absent		24	26	28	22	25	25	19	31	16	33
LEIOMYOMA	b	0	0	0	0	0	0	0	0	1	0

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

	Dose (ppm) 0		20		200		2000		4000	
	D	T	D	T	D	T	D	T	D	T
number of animals	24	26	28	22	25	25	19	31	17	33
Testis										
TESTICULAR TUMOURS										
absent	23	24	27	22	24	23	19	30	17	31
INTERSTITIAL CELL TUMOUR b	1	2	1	0	1	2	0	1	0	2
Thyroid										
THYROID TUMOUR										
absent	21	22	27	20	22	21	17	26	15	30
THYROID FOLLICULAR ADENOMA b	2	0	0	1	1	0	0	1	0	0
THYROID FOLLICULAR CARCINOMA m	0	0	0	0	0	1	1	1	0	0
THYROID F'FOLL. CELL ADENOMA b	1	4	1	1	1	3	1	3	2	3
Urinary bladder										
URINARY BLADDER TUMOUR										
absent	24	26	28	21	24	25	19	31	17	33
TRANSITIONAL CELL ADENOMA b	0	0	0	1	0	0	0	0	0	0

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		24	26	28	22	25	25	19	31	17	33
Non-protocol Organs											
Limb (left hind)											
CONNECTIVE TISSUE TUMOUR	m	-	-	-	-	-	0	-	-	1	-
SYNOVIAL SARCOMA	m	-	-	-	-	-	1	-	-	0	-
Lymph node, pancreatic											
HAEMANGIOSARCOMA	b	-	-	-	-	-	1	-	-	-	-
Mammary gland											
MAMMARY FIBROADENOMA	b	-	-	-	-	-	1	-	-	-	2
Pinna											
AMELANOTIC MELANOMA	b	-	-	-	-	-	-	-	1	-	-

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Male

	Dose (ppm) 0		20		200		2000		4000	
	D	T	D	T	D	T	D	T	D	T
number of animals	24	26	28	22	25	25	19	31	17	33
Overall Tumour Incidence										
PRIMARY TUMOURS										
absent	2	6	5	0	4	6	6	2	3	5
BENIGN TUMOUR	16	14	15	18	11	13	7	26	6	25
MALIGNANT TUMOUR	6	6	8	4	10	6	6	3	8	3
MULTIPLE PRIMARY TUMOURS										
absent	12	17	17	10	14	11	14	17	9	20
BENIGN TUMOUR	12	8	10	12	10	14	4	14	6	12
MALIGNANT TUMOUR	0	1	1	0	1	0	1	0	2	1

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Pathologist: J P Finn

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Female

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		34	16	28	22	27	23	34	16	31	19
Adrenal cortex											
CORTICAL TUMOURS											
absent		34	16	27	20	25	22	33	16	31	19
ADRENAL CORTICAL ADENOMA	b	0	0	1	1	0	1	1	0	0	0
ADRENAL CORTICAL CARCINOMA	m	0	0	0	1	1	0	0	0	0	0
Adrenal medulla											
MEDULLARY TUMOUR											
absent		31	15	27	20	25	22	33	14	29	17
PHAEOCHROMOCYTOMA	b	2	1	1	1	1	0	0	1	1	2
PARAGANGLIOMA	b	0	0	0	0	0	0	0	1	0	0
GANGLIONEUROMA	b	0	0	0	0	0	1	0	0	0	0
Bone											
ORAL CAVITY TUMOUR											
absent		34	15	28	22	27	23	34	16	31	19
SQUAMOUS CELL CARCINOMA	m	0	1	0	0	0	0	0	0	0	0
Brain											
CNS NEOPLASIA											
absent		34	16	28	22	27	23	33	16	31	18
ASTROCYTOMA	m	0	0	0	0	0	0	0	0	0	1
OLIGODENDROGLIOMA	m	0	0	0	0	0	0	1	0	0	0
Haemopoietic system											
LYMPHOMATOUS TUMOUR											
absent		34	16	28	22	26	23	34	16	31	19
PLASMACYTOMA	m	0	0	0	0	1	0	0	0	0	0
HISTIOCYTIC TUMOUR											
absent		34	16	27	21	27	22	34	16	31	19
HISTIOCYTIC SARCOMA	m	0	0	1	0	0	0	0	0	0	0
MONOCYTIC LEUKAEMIA	m	0	0	0	1	0	1	0	0	0	0
ARBITRARY PRIMARY, SECONDARIES ONLY PRESENT											
absent		33	16	27	22	27	23	34	16	31	19
CARCINOMA OF UNKNOWN ORIGIN	m	1	0	1	0	0	0	0	0	0	0
Jejunum											
SMOOTH MUSCLE TUMOURS											
absent		34	16	28	22	26	23	34	16	30	18
LEIOMYOMA	b	0	0	0	0	0	0	0	0	0	1
Kidney											
TUMOUR CONNECTIVE TISSUE											
absent		34	16	28	22	26	23	34	15	31	19
LIPOMA	b	0	0	0	0	0	0	0	1	0	0

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Female

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		34	16	28	22	27	23	34	16	31	19
Liver											
HEPATOCELLULAR TUMOURS											
absent		33	16	28	22	26	23	34	16	31	18
one HEPATOCELLULAR ADENOMA	b	1	0	0	0	0	0	0	0	0	1
Mammary gland											
MAMMARY TUMOUR, EPITHELIAL											
absent		17	5	11	10	9	5	18	6	14	4
one MAMMARY FIBROADENOMA	b	10	7	10	4	9	9	9	5	8	8
two MAMMARY FIBROADENOMAS	b	2	2	2	3	2	4	4	1	5	4
three MAMMARY FIBROADENOMAS	b	2	0	1	3	3	3	0	1	1	1
four MAMMARY FIBROADENOMAS	b	1	2	2	1	1	0	0	0	1	1
one MAMMARY ADENOCARCINOMA	m	4	0	3	2	5	4	5	1	3	1
two MAMMARY ADENOCARCINOMAS	m	2	0	1	1	0	0	0	0	1	0
three MAMMARY ADENOCARCINOMAS	m	0	0	1	0	0	0	0	1	0	0
four MAMMARY ADENOCARCINOMAS	m	0	0	1	0	0	0	0	0	0	0
one MAMMARY SARCOMA	m	0	0	1	0	0	0	0	0	0	0
Ovary											
OVARIAN TUMOURS											
absent		34	16	28	21	25	23	31	16	31	19
GRANULOSA CELL TUMOUR	b	0	0	0	0	0	0	1	0	0	0
THECOMA	b	0	0	0	0	0	0	1	0	0	0
GRANULOSA CELL TUMOUR	m	0	0	0	1	1	0	0	0	0	0
OVARIAN CARCINOMA	m	0	0	0	0	0	0	1	0	0	0
Pancreas											
absent		34	15	27	20	26	23	34	16	31	19
ISLET CELL ADENOMA	b	0	1	1	2	0	0	0	0	0	0
Pituitary											
PITUITARY TUMOUR											
absent		3	5	3	5	6	7	5	8	12	4
PARS DISTALIS ADENOMA	b	31	11	25	17	21	16	29	8	19	15
Skin											
EPITHELIAL SKIN TUMOURS											
absent		33	16	28	22	27	22	34	15	31	17
one PAPILLOMA	b	1	0	0	0	0	0	0	1	0	0
one KERATOACANTHOMA	b	0	0	0	0	0	1	0	0	0	1
one CLITORAL GLAND ADENOMA	b	0	0	0	0	0	0	0	0	0	1

Key : D = decedent T = terminal kill b = benign m = malignant
Pathologist: J P Finn

TOX/96294

Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Female

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		34	16	28	22	27	23	34	16	31	19
Skin											
CONNECTIVE TISSUE SKIN TUMOUR											
absent		32	14	27	20	26	22	33	16	29	19
one FIBROMA	b	1	0	1	0	0	1	1	0	0	0
one FIBROSARCOMA	m	1	1	0	0	0	0	0	0	1	0
one SARCOMA	m	0	0	0	0	1	0	0	0	0	0
one LIPOMA	b	0	0	0	2	0	0	0	0	0	0
two LIPOMAS	b	0	1	0	0	0	0	0	0	0	0
one AMELANOTIC MELANOMA	b	0	0	0	0	0	0	0	0	1	0
Thymus											
THYMIC NEOPLASM											
absent		32	14	26	22	26	21	32	15	29	17
LYMPHOMA (SINGLE ORGAN)	b	0	0	1	0	0	0	1	0	0	0
Thyroid											
THYROID TUMOUR											
absent		31	15	25	19	25	23	34	14	30	19
THYROID FOLLICULAR ADENOMA	b	1	0	1	0	0	0	0	0	0	0
THYROID F'FOLL. CELL ADENOMA	b	1	1	2	3	2	0	0	2	0	0
Tongue											
SKELETAL MUSCLE TUMOUR											
absent		33	16	28	21	27	23	34	16	30	19
GRANULAR MYOBLASTOMA	b	0	0	0	1	0	0	0	0	0	0
Uterus											
UTERINE CONNECTIVE TISSUE TUMOUR											
absent		34	16	27	22	27	23	32	16	30	19
LEIOMYOMA	b	0	0	1	0	0	0	2	0	0	0
LEIOMYOSARCOMA	m	0	0	0	0	0	0	0	0	1	0
EPITHELIAL UTERINE TUMOUR											
absent		32	16	28	21	27	23	32	15	29	19
ENDOMETRIAL CARCINOMA	m	1	0	0	1	0	0	2	1	2	0
SQUAMOUS CELL CARCINOMA	m	1	0	0	0	0	0	0	0	0	0

Key: D = decedent T = terminal kill b = benign m = malignant
Pathologist: J P Finn

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Female

		Dose (ppm) 0		20		200		2000		4000	
		D	T	D	T	D	T	D	T	D	T
number of animals		34	16	28	22	27	23	34	16	31	19
Non-protocol Organs											
Limb (left hind)											
OSTEOMA	b	-	-	-	1	-	-	-	-	-	-

Key D = decedent T = terminal kill b = benign m = malignant
Pathologist: J P Finn

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Table 4.6
INCIDENCE OF NEOPLASTIC MICROSCOPIC FINDINGS (TERMINAL KILL)

Female

	Dose (ppm) 0		20		200		2000		4000	
	D	T	D	T	D	T	D	T	D	T
number of animals	34	16	28	22	27	23	34	16	31	19
Overall Tumour Incidence										
PRIMARY TUMOURS										
absent	0	2	0	1	1	1	0	2	5	1
BENIGN TUMOUR	24	12	20	15	17	17	25	11	19	16
MALIGNANT TUMOUR	10	2	8	6	9	5	9	3	7	2
MULTIPLE PRIMARY TUMOURS										
absent	15	7	12	6	11	8	16	8	17	4
BENIGN TUMOUR	19	9	15	15	16	15	18	8	13	15
MALIGNANT TUMOUR	0	0	1	1	0	0	0	0	1	0

[redacted]

Key : D = decedent T = terminal kill b = benign m = malignant
Pathologist: J P Finn