DATA EVALUATION REPORT

AE F122006

STUDY TYPE: ONCOGENICITY FEEDING – MOUSE [OPPTS 870.4200 (§83-2b)]
MRIDs 44973801 and 44973802

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
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Task Order No. 00-30B

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237

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Registration Action Branch I

SCO 11/15/2000

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Feeding – Mouse;OPPTS [870.4200 (§83-2b)]

DP BARCODE: D253998
P.C. CODE: 999999

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

TEST MATERIAL (PURITY): AE F122006 (purity, 98.7% a.i.)

SYNONYMS: none

CITATION: Troschau, G. 1999. Mouse dietary oncogenicity (18 months study) AE F122006. Hoechst Marion Roussel Deutschland GmbH Drug Innovation & Approval Lead Optimization Department of Toxicology/Pathology, D-65926 Frankfurt am Main, Germany, AgrEvo UK Study No. TOX 94419 & Laboratory Project ID No. 97.0012, Report Nos. 99.0145 & TOX/99/252-66. October 21, 1999. MRIDs 44973801 and 44973802.

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

EXECUTIVE SUMMARY: In an oncogenicity study (MRIDs 44973801 and 44973802), AE F122006 (98.7 % a.i., batch no. CR 21492/03/950801) was administered to groups of 50 male and 50 female CD-1 mice in the diet at concentrations of 0, 12.5, 125, or 1250 ppm (MRID 44973801) and 0 or 2500 ppm (MRID 44973802). The combined results of these studies are discussed below. These concentrations resulted in a nominal compound intake for each concentration level of 1.67, 16.60, 169.63, or 336.85 mg/kg/day for males; 2.08, 19.88, 202.49, or 407.28 mg/kg/day for females for 12.5, 125, 1250, or 2500 ppm doses, respectively.

No treatment-related abnormal findings were observed with respect to inspections of general health, behavior, eyes, teeth, or oral mucosa. The palpations of the skin for nodules and masses revealed no treatment-related increase in incidences of findings among treatment groups compared to their respective control groups.

Mortality was slightly increased (16 %, n.s.) in males fed 1250 ppm compared to the control group and significantly increased ($p < 0.05$) 12 % and 20 % among males and females, respectively fed 2500 ppm. No specific cause for the increased mortality could be determined.

238

No treatment-related effects on body weight or food consumption were determined up to the highest dietary concentration in this study, 2500 ppm for males or females. Overall body weight gain among treated groups was comparable to the respective control groups.

Statistically significantly increased ($p < 0.05$) total leukocyte counts were observed in males and females fed 125 -2500 ppm. Other hematological alterations were considered incidental as they were not concentration related. All the observed hematological values for treatment groups were within the limits of historical controls and were not considered treatment related.

Organ weight alterations among treatment groups compared to the control groups for absolute and relative kidney, adrenal, and heart weights were observed. In the absence of a concentration-effect relationship and histopathological correlations, these were considered incidental to treatment.

An increase in the incidence of centrilobular hepatocyte hypertrophy was observed among male mice treated with 2500 ppm. There were no other toxicologically relevant histopathological findings.

The lowest-observed-adverse-effect-level (LOAEL) in this study was determined to be 1250 ppm for males (169.6 mg/kg/day for males) based on the slightly decreased survival of males at this dose and 2500 ppm for females (407.3 mg/kg/day for females) based on the significant decreased survival of females at this dose during the 18-month study. The no-observed-adverse-effect-level (NOAEL) for this study was determined to be 125 ppm for males (16.6 mg/kg/day in males) and 1250 ppm for females (202.5 mg/kg/day for females).

Treatment of CD-1 mice with AE F122006 in the diet for up to 18 months did not result in increased incidences of neoplasms in treated mice compared to the respective control groups. The most common neoplasms in aging mice were malignant lymphomas. Due to the increased intercurrent mortality rate in the 1250 and 2500 ppm groups, the animals were determined to have been adequately dosed.

This oncogenicity study in the mouse is **Acceptable/Guideline** and does satisfy the requirement for an oncogenicity study [OPPTS 870.4200 (§83-2b)] in mice.

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
   Description: white/pale cream solid
   Lot/Batch #: batch no. CR 21492/03/950801
   Purity: 98.7 % a.i.

Stability of compound: The compound was shown to be stable stored at 20°C in darkness for the duration of this study.
CAS #: not provided
Structure: not provided

2. Vehicle and/or positive control

The test material was mixed with feed; a positive control was not included in this study.

3. Test animals: Species: mouse

Strain: CD-1
Age and weight at study initiation: age: 5 - 6 weeks; mean body weight: males: 24.2 g; females: 21.1 g
Source: Charles River, Sulzfeld, Germany
Housing: individually in transparent macrolon® cages (type II), with soft wood granulate bedding
Diet: Powdered laboratory rodent diet, ssniff® (V1530)-diet, *ad libitum*
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 22 ± 3°C
Humidity: 50 ± 20 %
Air changes: 15/hour, in a positive pressure room
Photoperiod: 12 hours light/12 hours dark
Acclimation period: approx. 1 week

B. STUDY DESIGN

1. In life dates

Start: February 12, 1997; end: August 28, 1998

2. Animal assignment

Animals were assigned to the test groups in Table 1 by a method that ensured animals with similar weights were randomly distributed in all groups. Mice at extremes of the weight range were not included in the study.

TABLE 1. Study design					
Test group	Dietary concentration (ppm)	Dose to animals[a] (mg/kg/day)		Number of animals	
		Male	Female	Male	Female
1	0	0	0	50	50
2	12.5	1.67	2.08	50	50
3	125	16.60	19.88	50	50
4	1250	169.63	202.49	50	50
5[b]	2500	336.85	407.28	50	50

Data taken from p. 10, MRID 44973802

[a] Daily dietary consumption was calculated from the mean weekly food consumption and body weight data and was based on nominal dietary levels of test substance.

[b] This group was overdosed in the initial study, the second MRID 44973802 was conducted to repeat this concentration group and included a second untreated control group.

3. Dose selection

The dose selections were based on a previous 90-day feeding study utilizing mice. Administration of 2500 ppm of the test substance resulted in centrilobular hepatocyte enlargement and vacuolation in males. Increased fat deposition in the centrilobular region was observed in both males and females at this dose. Also at 2500 ppm, mean absolute kidney weight was decreased 26% in males and in females, both absolute and relative kidney weights were decreased 25 %. Therefore, the highest dose of 2500 ppm selected for this study was expected to serve as the maximum tolerated dose (MTD), 1250 ppm which is half the target MTD served as an alternate MTD in the case of an excessive toxic response at the highest dose. Ten-fold below the high-intermediate dose was the designated mid-dose, 125 ppm, and ten-fold below the mid-dose, 2.5 ppm, the lowest dose was expected to serve as a clear NOAEL.

4. Diet preparation and analysis

The test substance was premixed with the ground diet ssniff® at 1 or 4 week intervals. The final dietary mixtures were prepared from premixes for each dose group every 1 to 4 weeks by mixing the appropriate amount of diet with the premix and mixing in a precision mixer (Lödige Modell 20E and Lödige FM 130/D1ZF) for 30 minutes. Three separate samples were taken from the final mixtures of each dose level for concentration analysis. The homogeneity of the mixtures and the actual active ingredient content were determined by HPLC at 24, 36, 48, 60, and 72 weeks. The stability of the test compound in the diet was analyzed by determination of the nominal concentration of the test substance in the spiked diet at concentrations of 0, 6, or 2500 ppm.

241

Results –
Concentration and homogeneity – The achieved concentration and the homogeneous distribution of AE F122006 in the diet were confirmed as acceptable i.e., in the range of 81 to 112 %.

Stability – The stability of the test compound in the diet was confirmed as acceptable i.e. within the range of 82 to 102 % of nominal for 35 days.

5. Statistics

Effects on body weight, erythrocyte count, hemoglobin, hematocrit, MCV, reticulocyte count, leucocyte count, thrombocytes, absolute, and relative organ weights were evaluated by comparison of each treated group with the control group for 2-tailed significance. T-tests were used to evaluate differences for body weight and absolute organ weights, the Wilcoxon's test with the exact distribution according to Streitberg and Röhmel (1987) was used to evaluate relative organ weights and parameters of hematology. Comparisons were considered significant at $p < 0.05$. Incidences of histopathological neoplastic and non-neoplastic findings were evaluated by pair-wise analysis, Fisher's exact test, and trend analysis for neoplastic lesions and non-neoplastic lesions. Only p-values of less than 0.05 for rare lesions and p-values of less than 0.01 for common lesions were considered statistically significant. Trend analysis was performed only when significant differences were found by pair-wise comparison with Fisher's exact test.

C. METHODS

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality on week days, and once daily on weekends and holidays. Animals were examined monthly for neurological disturbances, impairment of dental growth, and changes in the eyes and oral mucosa. Also, each animal was palpated for masses once monthly during the first six months of treatment and twice monthly thereafter.

2. Body weight

Animals were weighed at weekly intervals throughout the study and at study termination.

3. Food consumption and compound intake

Food consumption for each animal was determined weekly throughout the study. The compound intake (mg/kg body weight) was calculated for each concentration from

mean food consumption and nominal dose levels. Food efficiency was not calculated in this study.

4. Ophthalmoscopic examination

Any findings concerning the lens or cornea were confirmed by ophthalmoscopic examination using a slit lamp (Zeiss hand slit lamp). Pupils were dilated prior to the examination by local administration of Mydriaticum Stulln® (manufactured by Pharma Stulln GmbH).

5. Blood was collected from the retrobulbar venous plexus of all surviving mice during weeks 53/54 and 79 - 81. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements		Red and white blood cell and platelet
	(Thromboplastin time)		morphology
	(Clotting time)		Red cell distribution width (RCDW)
	(Prothrombin time)		

* Minimum required for oncogenicity studies unless effects are observed, based on Subdivision F Guidelines.

b. Clinical chemistry

Clinical chemistry tests were not conducted and are not required for oncogenicity studies based on Subdivision F guidelines.

6. Urinalysis

Urinalysis tests were not conducted and are not required for oncogenicity studies based on Subdivision F guidelines.

7. Sacrifice and pathology

Necropsies were done on all animals that died or were killed at unscheduled times during the treatment period. At scheduled study termination, all surviving animals were killed by cervical dislocation and necropsied. The CHECKED (X) tissues from all groups were collected for histopathological examination. Tissue samples were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. All

collected tissues and gross lesions were examined by light microscopy from each treated and control group. The (XX) organs from all animals were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*
	Oral tissue	XX	Heart*	X	Periph. nerve* (Sciatic)
X	Salivary glands*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Esophagus*	X	Lymph nodes*	X	Pituitary*
X	Stomach*	XX	Spleen*	X	Eyes*
X	Duodenum*	X	Thymus*		
X	Jejunum*				GLANDULAR
X	Ileum*		UROGENITAL	XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+	X	Lacrimal/Harderian glands
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	X	Parathyroids*
XX	Liver*+	X	Epididymides	X	Thyroids*
X	Gall bladder*	X	Prostate		Auditory sebaceous gland
X	Pancreas*	X	Seminal vesicle		(Zymbal's gland)
			Coagulating gland		
	RESPIRATORY		Preputial gland		OTHER
X	Trachea*	XX	Ovaries*	X	Cartilage-Bone Junction*
X	Lung*	X	Uterus*	X	Skeletal muscle*
X	Diaphragm		Cervix	X	Skin*
	Pharynx	X	Oviduct		
X	Larynx	X	Vagina	X	All gross lesions and masses*
X	Ethmoid turbinals				

* Required for oncogenicity studies based on Subdivision F Guidelines.

+ Organ weight required in oncogenicity studies.

II. RESULTS

A. OBSERVATIONS

1. Toxicity

No treatment-related abnormal findings were observed with respect to inspections of general health, behavior, eyes, teeth, or oral mucosa. The palpations of the skin for nodules and masses revealed no treatment-related increased findings among treatment groups compared to their respective control groups.

2. Mortality

The percent mortality at selected times during the study is given in Table 2. There was no decrease in survival among treated females up to the 1250 ppm dietary concentration group. Males fed 1250 ppm and males and females in the 2500 ($p < 0.05$) ppm groups had increased mortality compared to the control groups. A specific reason for the increased mortality could not be determined by the study pathologist.

TABLE 2. Percent survival of male and female mice fed AE F122006 for 80 weeks

Weeks of study	Dietary concentration (ppm)					
	0[a]	0[b]	12.5	125	1250	2500
Males						
Week 1 - 26	0	0	0	0	2	0
Week 27 - 52	0	2	1	0	1	3
Week 53 - 78	5	7	6	7	10	12
total deaths	5	9	7	7	13	15
% mortality	10	18	14	14	26	30*
Females						
Week 1 - 26	0	0	1	0	0	1
Week 27 - 52	1	1	2	3	1	4
Week 53 - 78	9	5	11	11	12	11
total deaths	10	6	14	14	13	16
% mortality	20	12	28	28	26	32*

Data taken from p. 23, MRID 44973801 and p. 25, MRID 44973802
*$p < 0.05$, Significantly different from control
[a] Control data from MRID 44973801
[b] Control data from MRID 44973802

B. BODY WEIGHT

The group mean body weights in male and female mice over selected time periods during treatment are summarized in Table 3. There were no treatment-related effects on body weight among males and females fed AE F122006. Some sporadic statistically significant increases in mean body weight were observed, these differences were marginal and considered incidental. Overall mean body weight gain for all treatment groups was comparable to the respective control groups.

TABLE 3. Group mean body weights and body weight gains in male and female mice fed AE F122006 for up to 80 weeks (g)						
Days on study	Dietary concentration (ppm)					
	0[a]	0[b]	12.5	125	1250	2500
Males						
1	24.8	24.6	24.4	24.3	24.2	24.9
92	34.6	34.8	34.5	35.4*	35.0*	35.5
183	37.1	37.2	37.0	38.0	37.5	38.4
351	38.2	40.0	39.1*	40.3*	39.6*	39.4
547	40.3	39.2	39.7	41.3	40.8	39.7
Overall body wt. gain	15.5	14.6	15.3	17.0	16.6	14.8
Females						
1	21.0	20.4	21.3	21.4	21.0	20.3
92	28.2	27.3	28.8	29.2	28.4	27.3
183	30.2	28.1	29.8	30.3	30.0	28.8
351	30.7	29.7	30.6	31.8	31.3	30.9*
547	32.7	30.9	32.5	33.4	32.5	32.4*
Overall body wt. gain	11.7	10.5	11.2	12.0	11.5	12.1

Data taken from p. 24, MRID 44973801 and p. 26, MRID 44973802
*$p < 0.05$, Significantly different from control.
[a] Control data from MRID 44973801
[b] Control data from MRID 44973802

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

Food consumption values among treated groups were similar to their respective control groups.

2. Compound consumption

The compound consumption was calculated from the food consumption and nominal values from the dietary concentrations. The results are given in Table 1.

3. Food efficiency

Food efficiency was not calculated and does not appear to have been affected by the test substance since there was no treatment-related effect on body weight gain or on food consumption in this study.

4. Ophthalmoscopic examination

No ocular effects were noted during the physical examinations of the animals, therefore no ophthalmoscopic examinations were performed.

D. BLOOD WORK

1. Hematology

Total leukocyte counts were slightly but significantly ($p < 0.05$) increased in both sexes among groups treated with 125, 1250, or 2500 ppm at the final sacrifice. However, there were no significant differences in the differential blood counts of these animals. MCV values among males and females treated with 125 or 1250 ppm were slightly but significantly decreased. Females in the 1250 ppm treated group had a slightly but significantly decreased hematocrit and thrombocyte count compared to the controls; males in the 2500 ppm group had reticulocyte counts that were similarly affected. All values for hematological parameters were within the normal ranges for CD-1 mice and were not considered treatment-related.

TABLE 4. Group mean hematology parameter values in male and female mice fed AE F122006 for 80 weeks and historical controls.

Hematology parameter	Dietary concentration (ppm)							
	0[a]	0[b]	0[c]	0[d]	12.5	125	12500	2500
Males								
Total leukocyte count (10^{-9}/L)	4.8	2.7	3.9	2.9	3.2	4.0*	4.6*	5.5*
Females								
Total leukocyte count (10^{-9}/L)	3.4	2.5	3.4	2.5	2.7	4.4*	4.5*	4.6*

Data taken from p. 11, MRID 44973802.
* $p < 0.05$, Compared to the concurrent control group.
[a] Historical control data
[b] Historical control data
[c] Control data from MRID 44973801
[d] Control data from MRID 44973802

E. SACRIFICE AND PATHOLOGY

1. Organ weight

Females fed 1250 ppm had decreased (7 %, $p < 0.05$) absolute kidney weights compared to the control group. Males fed 2500 ppm had decreased (11 %, $p < 0.05$) absolute and relative kidney weights. Relative adrenal weights were reduced among males fed 1250 (14.2 %, $p < 0.05$) or 2500 (n.s.) ppm, and the absolute adrenal weight was reduced 23 % ($p < 0.05$) in males treated with 2500 ppm. Finally, females fed 1250 ppm had significantly decreased absolute (10.3 %, $p< 0.05$) and relative (9.7 %, $p < 0.05$) heart weights compared to the control group. These differences were inconsistent and not considered treatment related.

2. Gross pathology

A number of macroscopic findings were reported for animals in all treatment groups and in the control groups. These were not considered treatment related since they occurred with similar frequency in the control and treatment groups, were not dose-related, or were typical findings for CD-1 mice maintained under these laboratory conditions. Common macroscopic findings included: inflammation and/or hemorrhage of various organs, amyloidosis of various organs, granulocytosis of various organs, tubular casts in the kidneys, and colloid plugs in the urinary bladder.

3. Microscopic pathology

a. Non-neoplastic

Males and females treated with 12.5, 125, or 1250 ppm and females treated with 2500 ppm were not observed to have increased incidences of non-neoplastic lesions that could be attributed to the test substance. Centrilobular hepatocellular hypertrophy was observed in 10 males treated with 2500 ppm.

b. Neoplastic

A summary of the percentages of neoplasms seen in this study by dose group is given in Table 5. The most common lesions, and a leading cause of death in the aging mice, were malignant lymphomas. No treatment-related increases in the incidences of neoplastic lesions were seen in males or females fed AE F122006 for up to 18 months.

TABLE 5. Neoplastic lesion incidence in male and female mice fed AE F122006 for up to 18 months.

Parameter	Dietary concentration (ppm)					
	0[a]	0[b]	12.5	125	1250	2500
Males						
Percentage of animals with neoplasms	44	38	32	34	36	38
Percentage of animals with more than one primary neoplasm	8	12	6	2	12	12
Percentage of animals with metastases	0	4	2	0	0	0
Females						
Percentage of animals with neoplasms	54	60	34	46	36	60
Percentage of animals with more than one primary neoplasm	10	14	2	6	8	16
Percentage of animals with metastases	2	0	0	0	0	0

Data taken from p. 174, MRID 44973801 and p. 156, MRID 44973802

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSION

The investigators concluded that the dietary administration of up to 2500 ppm of AE F122006 to CD-1 mice for 80 weeks was not oncogenic. The author considered the NOEL (No observed effect level) to be 125 ppm (16.6 and 19.9 mg/kg/day in males and females, respectively) based on increased mortality at both 1250 and 2500 ppm.

B. REVIEWER'S DISCUSSION

Groups of 50 male and 50 female mice were fed AE F122006 in the diet at concentrations of 0, 12.5, 125, or 1250 ppm in MRID 44973801 and 0 or 2500 ppm in MRID 44973802. The combined results of these studies are discussed below.

General health, behaviour, the incidence of palpable masses, body weight changes, and food consumption were determined to be unaffected by the administration of the test substance at concentrations in the diet of up to 2500 ppm.

Survival in males and females fed 2500 ppm was statistically significantly decreased compared to the pooled controls of both studies. Males fed 1250 ppm had slightly increased mortality compared the control groups. No specific cause for the increased incidence of mortality could be determined.

Slightly, but statistically significantly increased total leukocyte counts were recorded for both males and females administered 125 ppm and higher. There was no pronounced concentration-effect relationship since all the treated groups had similar mean values. These differences were comparable with historical control data and therefore, were not considered treatment-related.

At necropsy there were some alterations in absolute and relative kidney, adrenal, and heart weights compared to the control groups. These findings were inconsistent with respect to concentration and in the absence of histopathological correlates were not considered treatment-related.

Histological evaluation of treated animals revealed only an increase in centrilobular hepatocyte hypertrophy in males fed 2500 ppm.

The lowest-observed-adverse-effect-level (LOAEL) in this study was determined to be 1250 ppm for males (169.6 mg/kg/day for males) based on the slightly decreased survival of males at this dose and 2500 ppm for females (407.3 mg/kg/day for females) based on the significant decreased survival of females at this dose during the 18-month study. The no-observed-adverse-effect-level (NOAEL) for this study was determined to be 125 ppm for males (16.6 mg/kg/day in males) and 1250 ppm for females (202.5 mg/kg/day for females)

Treatment of CD-1 mice with AE F122006 in the diet for up to 18 months did not result in increased incidences of neoplasms in treated mice compared to the respective control groups. The most common neoplasms in aging mice were malignant lymphomas. Due to the increased intercurrent mortality rate in the 1250 and 2500 ppm groups, the animals were determined to have been adequately dosed.

C. STUDY DEFICIENCIES

No major study deficiencies were identified. Detailed clinical examinations with palpations should be conducted once/week as required by Subdivision F guidelines. These determinations were made only once or twice per month in this study.

PATHOLOGY REPORT HMR Deutschland GmbH
SUMMARY TABLES

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
LUNGS	Examined:	50	50	50	50
- Carcinoma bron.-alv.		3	5	2	4
- Adenoma bronch.-alv.		1	1	-	4
- Met. ca. hepatocell.		-	1	-	-
CECUM	Examined:	45	44	42	41
- Adenoma		1	-	-	-
LIVER	Examined:	50	50	50	50
- Carcinoma hepatocell		4	2	4	4
- Hemangiosarcoma		1	1	-	-
- Adenoma hepatocell.		2	-	1	1
- Hemangioma		-	1	1	-
GALLBLADDER	Examined:	45	44	46	37
- Adenoma		-	1	-	-
KIDNEYS	Examined:	50	50	50	50
- Adenoma		-	1	-	-
- Harmatoma		-	1	-	-
TESTES	Examined:	50	50	49	50
- Adenoma leydig cell		2	-	-	-
EPIDIDYMIDES	Examined:	50	50	50	50
- Schwannoma malignant		-	-	1	-
PITUITARY GLAND	Examined:	43	42	45	40
- Adenoma pars dist.		-	-	1	-
THYROID GLAND	Examined:	49	50	49	48
- Adenoma follicular		-	-	1	-
ADRENAL CORTEX	Examined:	49	50	49	46
- Adenoma cortical		1	-	-	2
- Adenoma subcap. B c.		1	-	-	1
HEMOLYMPHORET. SYS.	Examined:	50	50	50	50
- Lymphoma malignant		5	3	3	3
SPLEEN	Examined:	50	50	50	50
- Hemangiosarcoma		-	-	-	1
- Hemangioma		-	-	1	-
THYMUS	Examined:	32	38	32	28
- Thymoma benign		1	-	-	-
HARDERIAN GLANDS	Examined:	50	50	50	50
- Adenocarcinoma		-	1	-	-
- Adenoma		4	2	2	2
SKIN/SUBCUTIS	Examined:	49	50	50	50
- Hemangiosarcoma		-	-	1	-
- Hemangioma		-	-	-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

252

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
LUNGS	Examined:	50	50	50	50
- Carcinoma bron.-alv.		2	2	2	-
- Adenoma bronch.-alv.		7	1*	2	3
- Met. tumor medullary		1	-	-	-
FORESTOMACH	Examined:	50	50	50	50
- Carcinoma squamous		-	-	-	1
LIVER	Examined:	50	50	50	50
- Adenoma hepatocell.		1	-	-	-
- Hemangioma		1	-	1	-
OVARIES	Examined:	50	49	49	50
- Cystadenoma		-	-	-	1
UTERUS	Examined:	50	50	50	50
- Adenocarcinoma		1	-	-	2
- Sarcoma end. stromal		1	-	1	1
- Adenoma		-	-	1	-
- Polyp endom.-stromal		1	-	-	-
- Hemangioma		-	-	1	-
PITUITARY GLAND	Examined:	43	41	39	34
- Adenoma pars dist.		1	-	-	-
- Ademoma pars interm.		-	1	-	-
THYROID GLAND	Examined:	50	49	48	47
- Adenoma follicular		-	-	-	1
- Adenoma C-cell		-	-	1	-
ADRENAL CORTEX	Examined:	50	50	49	50
- Met. tumor medullary		1	-	-	-
ADRENAL MEDULLA	Examined:	44	46	48	42
- Tumor medullary mal.		1	-	-	-
HEMOLYMPHORET. SYS.	Examined:	50	50	50	50
- Lymphoma malignant		11	10	17	10
- Leukemia granulocyt.		1	-	-	-
- Sarcoma histiocytic		3	2	1	1
HARDERIAN GLANDS	Examined:	50	46	49	46
- Adenoma		-	1	-	3
MAMMARY GLAND	Examined:	49	46	45	42
- Adenocarcinoma		1	1	-	-

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
GENERAL OBSERVATIONS	No.Examin	50	50	50	50
- Autolysis severe		3	1	2	7
- Autolysis		1	6	4	5
- Amyloidosis		3	9	8	7
CEREBRUM	No.Examin	50	50	50	50
- Inf. lymphoid cell		-	-	1	-
- Mineralization		5	1	5	5
- Hemorrhage		-	-	-	1
CEREBELLUM	No.Examin	50	50	47	49
- Hemorrhage		1	-	1	-
MEDULLA OBLONGATA	No.Examin	50	49	48	47
- Hemorrhage		4	-	3	-
- Degeneration axonal		-	-	2	1
SPINAL CORD, CERVIC.	No.Examin	47	47	43	41
- Hemorrhage		2	1	2	1
SPINAL CORD, THORAC.	No.Examin	49	47	48	48
- Degeneration axonal		-	-	-	1
- Hemorrhage		-	-	1	1
SPINAL CORD, LUMBAR	No.Examin	48	50	48	45
PERIPHER. NERVE(S)	No.Examin	49	49	49	48
- Myelinopathy degen.		1	-	1	2
HEART	No.Examin	50	50	50	50
- Fibrosis focal		-	2	-	-
- Inflammation		-	1	-	4
- Inf. lymphoid cell		3	2	1	-
- Arteritis/Periarter.		1	5	1	6
- Plaques bacterial		-	1	1	1
- Hyperplasia media		-	-	-	1
- Amyloidosis		2	7	5	5
- Thrombosis atrial		-	1	-	-
- Mineralization		-	-	-	2
AORTA	No.Examin	50	50	47	48
- Arteritis/Periarter.		-	1	-	-
NOSE	No.Examin	50	50	50	47
- Metapl. respiratory		-	-	-	1
- Inflammation exsuda.		-	-	2	1
- Inf. lymphoid cell		1	-	-	-
- Atrophy Bowman's gl.		1	-	-	-
- Eosinophil. globules		4	2	3	2
- Blood in nas. cavity		9	9	8	4
- Cyst(s)		-	1	-	-
LARYNX	No.Examin	49	50	49	48
- Hyperpl. epithelial		1	-	-	-
- Inflammation		1	-	-	-
- Amyloidosis		-	1	-	-
- Aspiration blood		8	2*	9	4
TRACHEA	No.Examin	46	50	50	44
- Inf. lymphoid cell		-	1	1	-
- Aspiration blood		9	7	5	5

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

254

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
LUNGS	No.Examin	50	50	50	50
- Hyperpl.·bron.-alv.		-	-	1	-
- Hyperplasia·BALT		-	1	-	-
- Inflammation·inter.		1	-	1	-
- Inf.·lymphoid cell		3	3	6	6
- Granulocytosis		2	-	1	3
- Alveolar macrophages		-	2	3	4
- Granuloma·foreign b.		-	1	1	-
- Amyloidosis		-	3	1	2
- Hemorrhage		17	4**	9	17
MEDIASTINUM	No.Examin	2	-	1	1
- Inf.·lymphoid cell		2	-	-	-
- Arteritis/Periarter.		-	-	-	1
TONGUE	No.Examin	50	50	50	50
- Inflammation		-	-	-	1
- Inf.·lymphoid cell		-	-	1	-
- Arteritis/Periarter.		-	2	1	1
- Amyloidosis		-	-	-	1
- Plaques·bacterial		-	-	-	1
- Parasites·sarcocysts		1	-	-	-
ESOPHAGUS	No.Examin	50	49	50	49
FORESTOMACH	No.Examin	50	50	50	50
- Hyperpl.·squamous c.		1	-	-	-
- Inf.·lymphoid cell		-	1	-	-
- Arteritis/Periarter.		-	-	-	1
- Amyloidosis		-	-	1	-
- Cyst(s)		1	-	-	2
GLANDULAR STOMACH	No.Examin	47	49	50	46
- Hyperplasia		8	6	5	6
- Inflammation		1	-	1	-
- Inf.·lymphoid cell		8	6	8	3
- Ulceration		-	-	1	-
- Amyloidosis		1	4	4	3
- Cyst(s)		-	1	-	1
DUODENUM	No.Examin	47	46	46	41
- Hyperpl.·avillous		-	-	1	-
- Hyperpl.·Brunner's		-	1	-	-
- Amyloidosis		1	6	5	3
- Cyst(s)		-	-	1	-
JEJUNUM	No.Examin	46	45	45	41
- Amyloidosis		1	5	6	6*
ILEUM	No.Examin	47	45	38	42
- Amyloidosis		6	9	7	6
CECUM	No.Examin	45	44	42	41
COLON	No.Examin	46	44	41	40
- Nematode(s)		-	1	3	-
RECTUM	No.Examin	45	44	43	37
MESENTERY	No.Examin	3	1	-	-
- Inf.·lymphoid cell		2	-	-	-

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
LIVER	No.Examin	50	50	50	50
- Focus clear cell		1	2	-	-
- Focus eosinophilic		-	1	-	-
- Focus baso. tigroid		-	1	-	-
- Focus baso. diffuse		1	-	-	2
- Inf. lymphoid cell		16	23	22	14
- Inf. granulocytic c.		1	-	-	-
- Kupffer-cell granul.		23	25	24	30
- Necrosis bridging		-	1	2	-
- Necrosis patchy		-	-	-	1
- Necrosis focal		1	-	-	1
- Necrosis lobular		-	-	-	1
- Remodelling lobular		-	1	-	-
- Angiectasia		-	1	-	-
- Fatty change centri.		-	-	-	1
- Fatty change perip.		-	-	-	1
- Amyloidosis		3	8	6	5
- Congestion		-	1	-	2
- Hematopoesis extram.		1	-	-	1
GALLBLADDER	No.Examin	45	44	46	37
- Inf. lymphoid cell		4	3	-	2
- Hemorrhage		-	-	-	1
PANCREAS	No.Examin	50	48	50	50
- Hyperpl. islet cell		8	14	12	3
- Hypertr. acinar cell		-	1	-	-
- Inf. lymphoid cell		8	4	5	5
- Inf. granulocytic c.		-	-	-	1
- Amyloidosis		1	1	1	-
- Necrosis focal		-	-	-	1
KIDNEYS	No.Examin	50	50	50	50
- Hyperplasia tubular		5	6	9	1
- Inflammation		2	-	1	1
- Inf. lymphoid cell		43	41	41	36
- Inf. plasam cell		-	-	-	1
- Abscess		-	1	-	-
- Arteritis/Periarter.		-	1	1	-
- Plaques bacterial		-	-	1	1
- Nephropathy chr. pr.		-	-	-	1
- Amyloidosis		3	9	8	7
- Tubular necrosis		-	-	-	1
- Tubular atrophy		21	17	20	17
- Tubular casts		36	36	27*	36
- Tubular fatty change		1	-	-	-
- Tub. mineralisation		1	1	2	2
- Fibrosis cortical		1	-	-	-
- Necrosis papillary		-	-	-	1
- Ectasia pelvis		2	-	-	-
- Cyst(s) cortical		8	6	9	15
URETERS	No.Examin	1	-	-	-
- Inflammation		1	-	-	-
URINARY BLADDER	No.Examin	50	49	50	47
- Mesen. proli. lesion		-	-	-	1
- Inf. lymphoid cell		14	15	21	15
- Inf. granulocytic c.		-	-	-	1
- Hemorrhage		-	-	-	1
- Colloid plug		15	23	33**	11

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

256

TEST ARTICLE : AE F122006
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SPONSOR : AgrEvo

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
TESTES	No.Examin	50	50	49	50
- Inf. lymphoid cell		1	-	-	-
- Arteritis/Periarter.		1	-	1	-
- Granuloma sperm		-	-	1	2
- Amyloidosis		2	7	5	7
- Atrophy tubular		12	8	12	14
- Mineraliz. tubular		2	2	2	3
- Thrombosis		-	-	-	1
- Cyst(s)		-	-	-	1
EPIDIDYMIDES	No.Examin	50	50	50	50
- Inflammation		1	-	-	1
- Inf. lymphoid cell		7	8	7	4
- Inf. granulocytic c.		-	-	-	1
- Granuloma sperm		1	4	-	1
- Arteritis/Periarter.		1	-	-	2
- Oligospermia		7	6	7	7
- Aspermia		3	5	7	4
- Debris spermatic		6	10	7	7
PROSTATE	No.Examin	50	50	47	47
- Hyperplasia		1	-	1	-
- Inflammation		1	-	1	2
- Inf. lymphoid cell		8	14	7	11
- Arteritis/Periarter.		-	-	-	1
SEMINAL VESICLES	No.Examin	50	50	50	49
- Inflammation		1	-	-	-
- Inf. lymphoid cell		1	3	-	2
- Devoid of colloid		-	-	1	1
PITUITARY GLAND	No.Examin	43	42	45	40
- Hypertr. pars dist.		-	1	-	-
- Cyst(s) colloid		2	2	2	-
THYROID GLAND	No.Examin	49	50	49	48
- Hyperpl. follicular		-	-	-	1
- Hyperpl. C-cell foc.		1	-	-	-
- Inflammation		1	1	-	1
- Inf. lymphoid cell		6	4	1	3
- Arteritis/Periarter.		-	-	1	-
- Amyloidosis		3	7	5	4
PARATHYROID GLANDS	No.Examin	48	46	47	39
- Inf. lymphoid cell		-	-	1	1
- Amyloidosis		3	6	5	3
- Cyst(s) ultimobran.		-	-	-	1
ADRENAL CORTEX	No.Examin	49	50	49	46
- Hyperpl. cortical		1	-	1	-
- Hyperpl. foc. A-cell		-	-	-	1
- Hyperpl. foc. B-cell		-	-	-	1
- Hyperpl. A-cell dif.		17	12	18	14
- Hypertrophy cortical		-	1	2	4
- Inf. lymphoid cell		-	-	-	1
- Amyloidosis		3	9	6	7
- Fatty change focal		3	4	6	2
- Atrophy		-	-	1	-
ADRENAL MEDULLA	No.Examin	47	48	47	41
HEMOLYMPHORET. SYS.	No.Examin	50	50	50	50

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
SPLEEN	No.Examin	50	50	50	50
- Inflammation		-	1	-	1
- Megakaryocytosis		4	6	4	7
- Amyloidosis		2	7	2	4
- Atrophy		2	4	4	1
- Depletion lymphocyte		2	-	-	1
- Plaques bacterial		-	-	-	1
- Congestion		-	1	-	-
- Erythropoesis extra.		2	6	6	1
- Myelopoesis extramed		3	-	1	-
BONE MARROW	No.Examin	50	50	50	50
- Granulopoesis incre.		2	-	3	1
- Congestion sinus		1	-	-	-
- Myelophthisis focal		1	1	1	-
THYMUS	No.Examin	32	38	32	28
- Hyperpl. tub.+ cords		1	2	1	1
- Hyperpl. lymphoid		1	-	-	-
- Arteritis/Periarter.		-	-	-	1
- Thrombosis		-	-	-	1
- Atrophy		-	-	-	3
- Cyst(s)		4	-	2	-
- Cyt(s) thyroglossal		-	-	-	1
LYMPH NODES	No.Examin	-	-	1	1
- Hyperpl. lymphoid		-	-	1	-
MESENT. LYMPH NODE	No.Examin	48	47	42	42
- Inflammation		-	-	-	1
- Hyperpl. lymphoid c.		1	-	-	-
- Granulocytosis		2	1	-	-
- Histiocytosis		-	-	-	1
- Amyloidosis		3	8	7	3
- Hemorrhage		2	2	2	2
ILIAC LYMPH NODE	No.Examin	46	46	39	33
- Inflammation		1	-	-	2
- Hyperpl. lymphoid		1	-	-	-
- Hyperpl. plasma cell		-	-	1	-
- Granulocytosis		2	3	1	1
- Megakaryocytosis		4	10	1	1
- Amyloidosis		1	4	1	3
- Hemorrhage		1	1	-	1
- Ectasia sinusoidal		-	-	1	-
MANDIBULAR LYMPH NO.	No.Examin	49	48	46	41
- Hyperpl. plasma cell		1	1	1	1
- Granulocytosis		1	-	-	-
- Amyloidosis		2	5	1	2
- Hemorrhage		4	3	5	5
PAROTID GLANDS	No.Examin	50	50	50	48
- Inf. lymphoid cell		2	3	5	5
- Amyloidosis		4	8	6	7
- Atrophy focal		-	2	-	-
SUBLINGUAL GLANDS	No.Examin	49	48	50	46
- Inf. lymphoid cell		2	-	1	2
- Amyloidosis		-	2	-	-

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
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MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
SUBMANDIBULAR GLANDS	No.Examin	50	50	50	50
- Inf. lymphoid cell		19	19	26	23
- Arteritis/Periarter.		-	-	1	-
- Amyloidosis		-	1	-	-
- Atrophy focal		1	-	1	-
HARDERIAN GLANDS	No.Examin	50	50	50	50
- Inflammation		1	-	-	-
- Inf. lymphoid cell		17	16	18	13
- Inf. plasma cell		-	-	-	1
- Degeneration		3	5	5	2
- Amyloidosis		1	-	1	-
- Atrohpy focal		-	-	-	1
EXORBITAL LACR.GLDS.	No.Examin	47	35	46	39
- Inf. lymphoid cell		22	16	17	13
- Arteritis/Periarter.		-	-	1	-
- Amyloidosis		1	4	6	2
- Hypertrophy		-	-	-	1
- Alteration Harderian		1	-	-	-
- Atrophy focal		-	-	1	-
SKIN/SUBCUTIS	No.Examin	49	50	50	50
- Inflammation dermis		1	1	-	-
- Granuloma		1	-	-	-
- Hemorrhage		1	-	-	1
SKELETAL MUSCLE	No.Examin	50	49	49	49
- Inflammation		1	-	-	-
- Inf. lymphoid cell		-	2	1	-
- Arteritis/Periarter.		2	1	1	-
- Degeneration		-	-	1	2
- Parasites sarcocysts		3	-	-	-
DIAPHRAGM	No.Examin	50	50	50	48
- Reaction mesothelial		-	-	-	1
- Degeneration		-	-	-	1
- Parasites sarcocysts		3	-	-	-
EYES	No.Examin	50	50	50	49
- Inflammation uvea		-	-	-	1
- Atrophy retina		-	1	-	-
- Degeneration lens		5	2	-	1
- Mineralization corn.		-	-	1	-
- Hemorrhage		-	1	-	-
OPTIC NERVES	No.Examin	49	46	45	42
- Myelinopathy degen.		-	1	-	-
EARS	No.Examin	10	10	9	5
- Hemorrhage		1	-	-	-
JOINT - FEMUROTIBIAL	No.Examin	49	50	49	47
- Inflammation		-	-	1	-
- Fibro-osseus lesion		-	1	-	-
- Arthropathy degener.		-	1	1	-
STERNUM	No.Examin	49	50	50	50

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
GENERAL OBSERVATIONS	No.Examin	50	50	50	50
- Autolysis severe		4	9	10	4
- Autolysis		4	4	3	8
- Amyloidosis		6	6	15*	10
CEREBRUM	No.Examin	50	50	50	50
- Inf. lymphoid cell		-	1	-	-
- Arteritis/Periarter.		-	-	-	1
- Malacia focal		1	-	-	-
- Mineralization		1	2	1	-
CEREBELLUM	No.Examin	50	49	44	49
- Hemorrhage		-	-	-	1
MEDULLA OBLONGATA	No.Examin	48	48	50	48
- Hemorrhage		3	2	1	-
- Degeneration axonal		2	1	-	-
SPINAL CORD, CERVIC.	No.Examin	39	42	36	32
- Malacia focal		-	1	-	-
- Hemorrhage		1	-	2	-
SPINAL CORD, THORAC.	No.Examin	49	49	47	39
- Hemorrhage		-	-	1	-
- Cyst(s) squamous		-	-	1	-
SPINAL CORD, LUMBAR	No.Examin	44	45	40	33
PERIPHER. NERVE(S)	No.Examin	46	47	46	46
- Myelinopathy degen.		1	-	-	2
HEART	No.Examin	50	50	50	50
- Inflammation		1	-	-	-
- Inf. lymphoid cell		-	1	2	-
- Arteritis/Periarter.		2	1	-	4
- Necrosis		-	1	-	-
- Amyloidosis		4	4	14**	9
- Thrombosis atrial		-	1	-	-
- Mineralization		-	1	-	-
AORTA	No.Examin	45	47	46	46
- Inf. lymphoid cell		-	1	-	-
- Arteritis/Periarter.		1	-	-	-
NOSE	No.Examin	49	49	50	49
- Hyperplasia		-	1	-	-
- Inflammation exsuda.		1	-	-	-
- Inflammation suppur.		-	1	-	-
- Eosinophil. globules		10	3*	5	4
- Blood in nas. cavity		7	6	5	7
- Fibro-osseus lesion		-	4	-	-
- Cyst(s)		-	1	-	-
LARYNX	No.Examin	50	47	42	47
- Inflammation		2	-	-	2
- Inf. lymphoid cell		3	2	-	3
- Arteritis/Periarter.		-	-	-	1
- Aspiration blood		13	8	6	6

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

260

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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1	D1	D2	D3
TRACHEA	No.Examin	49	45	47	37
- Inflammation		-	1	-	-
- Inf.·lymphoid cell		-	1	1	-
- Aspiration·blood		7	7	6	8
LUNGS	No.Examin	50	50	50	50
- Hyperpl.·bron.-alv.		2	-	2	-
- Ectasia·bronchial		-	-	1	-
- Metaplasia·osseus		-	-	1	-
- Inflammation·inter.		-	-	1	1
- Inf.·lymphoid cell		8	8	5	7
- Granulocytosis		2	1	2	4
- Alveolar macrophages		-	1	2	-
- Amyloidosis		-	-	1	-
- Hemorrhage		9	7	5	9
MEDIASTINUM	No.Examin	1	4	3	-
- Inflammation		1	-	1	-
- Inf.·lymphoid cell		-	3	1	-
TONGUE	No.Examin	50	50	48	50
- Inflammation		2	-	-	-
- Inf.·lymphoid cell		1	2	1	-
- Arteritis/Periarter.		2	1	1	2
- Edema		-	1	-	-
- Degeneration		1	-	-	-
ESOPHAGUS	No.Examin	50	50	50	48
- Inf.·lymphoid cell		-	-	-	1
- Food in lumen		1	-	-	-
FORESTOMACH	No.Examin	50	50	50	50
- Inflammation		-	-	-	1
- Arteritis/Periarter.		-	-	-	1
GLANDULAR STOMACH	No.Examin	49	46	45	49
- Hyperplasia		5	6	4	5
- Inf.·lymphoid cell		4	5	1	3
- Arteritis/Periarter.		1	1	-	1
- Amyloidosis		2	4	9*	3
- Cyst(s)		3	-	4	3
DUODENUM	No.Examin	44	38	38	41
- Arteritis/Periarter.		-	-	-	1
- Amyloidosis		6	3	9	6
JEJUNUM	No.Examin	44	39	39	43
- Amyloidosis		5	3	9	8
ILEUM	No.Examin	38	35	41	38
- Amyloidosis		10	9	10	9
CECUM	No.Examin	43	36	35	38
- Arteritis/Periarter.		-	-	-	1
COLON	No.Examin	41	38	37	38
- Amyloidosis		-	-	-	1
RECTUM	No.Examin	40	40	38	39

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

261

PATHOLOGY REPORT HMR Deutschland GmbH
SUMMARY TABLES

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
MESENTERY	No.Examin	7	4	6	12
- Inflammation		1	-	-	-
- Inf.-lymphoid cell		5	3	2	3
- Arteritis/Periarter.		1	-	-	3
LIVER	No.Examin	50	50	50	50
- Inf.-lymphoid cell		18	13	15	15
- Kupffer-cell granul.		33	30	28	33
- Necrosis-centrilob.		1	-	-	-
- Necrosis-focal		1	1	1	1
- Fatty change-centri.		1	-	-	-
- Fatty change-bridge.		-	1	-	-
- Amyloidosis		5	5	12	9
- Congestion		-	1	-	-
- Hematopoesis-extram.		3	1	-	-
- Hyperpl.-bile duct		-	-	1	-
- Cyst(s)-bile duct		-	-	1	-
GALLBLADDER	No.Examin	42	41	42	33
- Inflammation		-	1	-	-
- Inf.-lymphoid cell		7	8	4	6
- Arteritis/Periarter.		-	-	1	-
PANCREAS	No.Examin	50	49	47	50
- Hyperpl.-islet cell		7	8	9	6
- Inflammation		1	-	-	-
- Inf.-lymphoid cell		7	7	8	9
- Arteritis-periarter.		1	-	-	1
- Necrosis-focal		-	1	-	-
KIDNEYS	No.Examin	50	50	50	50
- Hyperplasia-tubular		3	5	4	4
- Inf.-lymphoid cell		34	35	24*	36
- Arteritis/Periarter.		1	-	-	-
- Nephropathy-chr.-pr.		-	1	1	1
- Amyloidosis		7	6	16*	10
- Tubular atrophy		7	11	8	2
- Tubular casts		21	19	24	21
- Tubular vacuolation		-	-	-	2
- Tub. mineralisation		1	-	-	-
- Necrosis-papillary		-	-	1	1
- Ectasia-pelvis		-	-	-	1
- Hyal. resorp. bodies		-	1	-	-
- Lipofuscin-diffuse		2	-	-	-
- Cyst(s)-medullary		2	-	-	-
- Cyst(s)-cortical		8	4	1*	1*
URINARY BLADDER	No.Examin	45	45	42	38
- Inflammation		-	-	1	-
- Arteritis/Periarter.		2	-	-	2
- Inf.-lymphoid cell		28	21	19	22
OVARIES	No.Examin	50	49	49	50
- Hyperpl.-sex cord-f.		-	-	-	1
- Cyst(s)		22	28	21	26
- Inflammation		1	-	-	-
- Inf. lymphoid cell		-	-	-	1
- Hemorrhage		1	-	1	-
- Amyloidosis		8	5	14	9
OVIDUCTS	No.Examin	48	47	47	47

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

262

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
UTERUS	No.Examin	50	50	50	50
- Hyperpl.·glandular		43	40	34*	37
- Decidual reaction		-	-	1	-
- Inf.·lymphoid cell		-	3	-	1
- Endometritis		1	1	-	1
- Pyometra		-	2	-	-
- Arteritis/Periarter.		2	-	1	1
- Hemorrhage		1	3	2	1
- Amyloidosis		-	-	2	-
- Cyst(s)·serosal		1	-	-	-
VAGINA	No.Examin	44	49	45	48
- Hemorrhage		1	1	-	-
PITUITARY GLAND	No.Examin	43	41	39	34
- Hyperpl.·pars dist.		1	-	1	-
- Hyperpl.·pars inter.		-	-	-	1
- Cyst(s)		1	-	-	-
- Cyst(s)·colloid		-	1	-	-
THYROID GLAND	No.Examin	50	49	48	47
- Hyperpl.·follicular		3	4	2	1
- Hyperpl.·C-cell·foc.		-	1	-	-
- Inflammation		6	2	-	1
- Inf.·lymphoid cell		12	9	8	8
- Arteritis/Periarter.		2	1	-	2
- Amyloidosis		6	6	13	8
PARATHYROID GLANDS	No.Examin	48	48	44	38
- Inf.·lymphoid cell		1	1	3	-
- Amyloidosis		6	5	11	7
ADRENAL CORTEX	No.Examin	50	50	49	50
- Hyperpl.·cortical		-	1	-	-
- Hyperpl.·foc.·A-cell		-	-	1	-
- Hyperpl.·A-cell·dif.		45	39	42	43
- Inf.·lymphoid cell		1	-	-	-
- Amyloidosis		8	3	14	6
ADRENAL MEDULLA	No.Examin	44	46	48	42
- Mineralization·medu.		1	-	-	-
HEMOLYMPHORET. SYS.	No.Examin	50	50	50	50
SPLEEN	No.Examin	49	50	48	48
- Hyperpl.·marginal z.		-	3	2	1
- Megakaryocytosis		6	7	9	1
- Amyloidosis		1	2	10**	5
- Atrophy		3	4	7	6
- Depletion·lymphocyte		5	-	-	1
- Erythropoesis·extra.		8	4	5	10
- Myelopoesis·extramed		5	1	-	7
- Storage·brown pigm.		-	-	-	1
BONE MARROW	No.Examin	50	50	47	50
- Granulopoesis·incre.		2	1	-	3
- Congestion·sinus		-	1	2	-
- Myelophthisis·focal		7	4	6	4
THYMUS	No.Examin	35	37	32	34
- Hemorrhage		2	-	1	2
- Cyst(s)		1	-	-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

263

TEST ARTICLE : AE F122006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : AgrEvo

PATHOL. NO.: 02946 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
LYMPH NODES	No.Examin	-	3	2	2
- Hematopoesis extram.		-	1	-	-
- Ectasia sinusoidal		-	1	-	-
MESENT. LYMPH NODE	No.Examin	43	40	34	37
- Granulocytosis		1	1	-	-
- Amyloidosis		3	4	7	3
- Hemorrhage		3	1	1	-
- Mineralization		-	-	1	-
ILIAC LYMPH NODE	No.Examin	39	38	35	34
- Hyperpl. lymphoid		-	-	1	-
- Granulocytosis		3	1	-	1
- Megakaryocytosis		-	1	-	-
- Amyloidosis		-	1	3	1
- Hematopoesis extram.		-	1	-	-
MANDIBULAR LYMPH NO.	No.Examin	47	48	47	42
- Hyperpl. lymphoid		1	-	1	-
- Granulocytosis		-	1	-	-
- Histiocytosis		1	-	-	-
- Amyloidosis		1	3	6	6*
- Hemorrhage		5	2	6	1
PAROTID GLANDS	No.Examin	50	50	50	47
- Inf. lymphoid cell		11	3*	6	1**
- Focus basophilic		2	-	-	-
- Amyloidosis		7	5	15*	9
SUBLINGUAL GLANDS	No.Examin	49	46	49	43
- Inf. lymphoid cell		4	-	7	3
- Arteritis/Periarter.		-	-	-	1
- Atrophy focal		-	1	-	-
- Amyloidosis		-	-	2	-
SUBMANDIBULAR GLANDS	No.Examin	50	49	50	49
- Inf. lymphoid cell		26	16*	23	18
- Arteritis/Periarter.		-	-	-	1
- Amyloidosis		1	-	2	-
- Atrophy focal		-	-	-	1
HARDERIAN GLANDS	No.Examin	50	46	49	46
- Inf. lymphoid cell		22	22	18	18
- Degeneration		-	1	1	1
EXORBITAL LACR.GLDS.	No.Examin	25	27	27	20
- Inf. lymphoid cell		10	10	6	6
- Amyloidosis		2	-	1	-
- Alteration Harderian		-	2	-	-
MAMMARY GLAND	No.Examin	49	46	45	42
- Inflammation		-	-	-	1
- Infil. lymphoid cell		1	4	-	1
- Granuloma foreign b.		-	1	-	-
- Lactation		10	5	5	-
SKIN/SUBCUTIS	No.Examin	50	50	48	49
- Hyperpl. squamous c.		-	-	-	1
- Inflammation dermis		2	1	-	1
- Edema		1	-	-	-

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

PATHOLOGY REPORT HMR Deutschland GmbH — PAGE : 39/1102
SUMMARY TABLES — 97.0012

TEST ARTICLE : AE F122006 — *PATHOL. NO.* : 02946 BUB
TEST SYSTEM : MOUSE, 18 months, oral — *DATE* : 19-JUL-99
SPONSOR : AgrEvo — *PathData® System V4.1C*

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C1 50	D1 50	D2 50	D3 50
SKELETAL MUSCLE	No.Examin	47	48	48	49
- Inflammation		1	-	-	1
- Arteritis/Periarter.		2	1	1	1
- Degeneration		1	-	-	-
- Atrophy		2	-	-	-
- Mineralization		-	-	1	1
- Parasites-sarcocysts		-	-	1	1
DIAPHRAGM	No.Examin	47	49	48	46
- Inflammation		-	-	-	1
- Inf.-lymphoid cell		-	1	-	-
- Arteritis/Periarter.		-	-	-	1
- Reaction-mesothelial		2	2	-	-
- Parasites-sarcocysts		-	-	-	1
ADIPOSE TISSUE	No.Examin	1	-	-	-
- Necrosis-focal		1	-	-	-
EYES	No.Examin	50	50	48	50
- Arteritis/Periarter.		-	-	-	1
- Atrophy-retina		2	2	-	1
- Degeneration-lens		-	1	-	1
- Mineralization-corn.		-	-	-	1
- Mineralization-uvea		-	-	1	-
OPTIC NERVES	No.Examin	41	33	33	39
- Atrophy		-	-	-	2
EARS	No.Examin	9	10	10	9
JOINT - FEMUROTIBIAL	No.Examin	50	50	50	46
- Fibro-osseus lesion		2	3	1	-
- Arthropathy-degener.		-	1	1	-
STERNUM	No.Examin	50	50	50	50
- Fibro-osseus lesion		1	4	1	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C1,

265

PATHOLOGY REPORT HMR Deutschland GmbH PAGE : 20/596
SUMMARY TABLES 97.0474

TEST ARTICLE : AE F122 006 *PATHOL. NO.*: 90004 BUB
TEST SYSTEM : MOUSE, 18 months, oral *DATE* : 19-JUL-99
SPONSOR : HOECHST *PathData® System V4.1C*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

	SEX :		MALE
	DOSE GROUP :	C2	D4
ORGAN/FINDING	NO. ANIMALS :	50	50
BRAIN	Examined:	1	-
- Astrocytoma·malig.	:	1	-
CEREBRUM	Examined:	49	50
- Inv.·astrocytoma·mal	:	1	-
LUNGS	Examined:	49	50
- Carcinoma·bron.-alv.	:	2	7
- Adenoma·bronch.-alv.	:	3	-
- Met.·t.·site unknown	:	1	-
LIVER	Examined:	50	50
- Carcinoma·hepatocell	:	3	6
- Adenoma·hepatocell.	:	1	1
- Hemangioma	:	-	1
KIDNEYS	Examined:	50	50
- Carcinoma	:	-	1
ADRENAL CORTEX	Examined:	49	48
- Adenoma·subcap.·B c.	:	1	-
HEMOLYMPHORET. SYS.	Examined:	50	49
- Lymphoma·malignant	:	11	5
SPLEEN	Examined:	49	48
- Hemangioma	:	-	1
HARDERIAN GLANDS	Examined:	49	49
- Adenoma	:	2	2
SKIN/SUBCUTIS	Examined:	49	50
- Hemangiosarcoma	:	1	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

266

TEST ARTICLE : AE F122 006 *PATHOL. NO.*: 90004 BUB
TEST SYSTEM : MOUSE, 18 months, oral *DATE* : 19-JUL-99
SPONSOR : HOECHST *PathData® System V4.1C*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
LUNGS	Examined:	50	50
- Carcinoma bron.-alv.		2	3
- Adenoma bronch.-alv.		2	2
OVARIES	Examined:	50	47
- Cystadenoma		2	-
UTERUS	Examined:	50	50
- Sarcoma end. stromal		1	-
- Leiomyosarcoma		1	1
- Schwannoma malignant		1	1
- Leiomyoma		1	2
PITUITARY GLAND	Examined:	41	40
- Adenoma pars dist.		1	1
- Ademoma pars interm.		1	1
HEMOLYMPHORET. SYS.	Examined:	50	50
- Lymphoma malignant		22	22
- Sarcoma histiocytic		-	4
THYMUS	Examined:	34	28
- Thymoma benign		3	-
MANDIBULAR LYMPH NO.	Examined:	47	40
- Hemangioma		1	-
HARDERIAN GLANDS	Examined:	50	50
- Adenoma		2	1
SKIN/SUBCUTIS	Examined:	50	47
- Keratoacanthoma		1	-
- Lipoma		-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

267

TEST ARTICLE : AE F122 006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : HOECHST

PATHOL. NO.: 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
GENERAL OBSERVATIONS	No.Examin	50	50
- Autolysis·severe		3	6
- Autolysis		6	9
- Amyloidosis		8	8
BRAIN	No.Examin	1	-
CEREBRUM	No.Examin	49	50
- Mineralization		5	5
CEREBELLUM	No.Examin	41	45
- Hemorrhage		3	2
MEDULLA OBLONGATA	No.Examin	42	45
- Hemorrhage		5	4
SPINAL CORD, CERVIC.	No.Examin	43	43
- Hemorrhage		-	1
SPINAL CORD, THORAC.	No.Examin	48	45
SPINAL CORD, LUMBAR	No.Examin	46	47
- Hemorrhage		1	-
PERIPHERAL NERVE(S)	No.Examin	46	48
- Degen. myelinopathy		-	1
HEART	No.Examin	50	50
- Fibrosis·focal		1	-
- Inflammation		2	1
- Inf.·lymphoid cell		-	1
- Inf.·granulocytic c.		-	1
- Arteritis/Periarter.		-	1
- Plaques·bacterial		1	-
- Amyloidosis		8	7
- Thrombosis·atrial		-	1
- Mineralization		1	-
AORTA	No.Examin	46	46
- Inf.·lymphoid cell		1	-
NOSE	No.Examin	48	48
- Hyperplasia		1	-
- Eosinophil. globules		2	1
- Blood in nas. cavity		9	6
- Fibro-osseus lesion		1	1
- Osteoporosis		1	-
LARYNX	No.Examin	38	39
- Inf.·lymphoid cell		2	4
- Aspiration·blood		10	5
TRACHEA	No.Examin	47	44
- Aspiration·blood		4	5

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

262

PATHOLOGY REPORT HMR Deutschland GmbH
SUMMARY TABLES

TEST ARTICLE : AE F122 006
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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2	D4
LUNGS	No.Examin	49	50
- Hyperpl.·bron.-alv.		-	3
- Hyperplasia·BALT		3	1
- Inflammation·bro-al.		1	2
- Hypertrophy·alveolar		1	-
- Inf.·lymphoid cell		2	2
- Granulocytosis		3	4
- Alveolar macrophages		1	2
- Amyloidosis		6	5
- Hemorrhage		14	10
- Edema·alveolar		-	1
- Emphysema·alveolar		1	-
TONGUE	No.Examin	49	50
- Inf.·lymphoid cell		-	1
- Arteritis/Periarter.		1	-
ESOPHAGUS	No.Examin	48	49
FORESTOMACH	No.Examin	50	50
- Inflammation		1	-
- Inf.·lymphoid cell		-	1
GLANDULAR STOMACH	No.Examin	49	44
- Hyperplasia		7	11
- Metapl.·squamous		-	1
- Inf.·lymphoid cell		4	2
- Erosion		1	-
- Amyloidosis		6	4
- Ectasia·glandular		2	2
- Cyst(s)		2	-
DUODENUM	No.Examin	45	37
- Arteritis/Periarter.		1	-
- Amyloidosis		8	2
JEJUNUM	No.Examin	46	37
- Amyloidosis		8	2
ILEUM	No.Examin	40	36
- Amyloidosis		9	4
- Invagination		-	1
CECUM	No.Examin	42	39
- Inflammation		1	-
- Arteritis/Periarter.		1	-
- Amyloidosis		-	1
- Edema		1	-
COLON	No.Examin	40	38
- Nematode(s)		6	3
RECTUM	No.Examin	39	38
- Inflammation		1	-
- Edema		-	1
MESENTERY	No.Examin	4	1
- Inf.·lymphoid cell		1	1
- Hemorrhage		1	-
- Amyloidosis		2	-

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

269

TEST ARTICLE : AE F122 006
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SPONSOR : HOECHST

PATHOL. NO.: 90004 BUB
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PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
LIVER	No.Examin	50	50
- Focus·clear cell		-	2
- Hypertrophy·hepatoc.		2	10*
- Mitosis		1	2
- Inf.·lymphoid cell		23	16
- Granulocytosis		-	2
- Kupffer-cell granul.		24	24
- Necrosis·centrilob.		-	1
- Necrosis·bridging		-	1
- Necrosis·focal		-	2
- Angiectasia		1	-
- Fatty change·centri.		1	-
- Fatty change·diffuse		-	1
- Amyloidosis		8	8
- Hematopoesis·extram.		1	-
GALLBLADDER	No.Examin	40	40
- Inf.·lymphoid cell		8	3
PANCREAS	No.Examin	49	48
- Hyperpl.·islet cell		10	14
- Inf.·lymphoid cell		8	10
- Atrophy·lobular		1	-
KIDNEYS	No.Examin	50	50
- Hyperplasia·tubular		8	7
- Inf.·lymphoid cell		37	39
- Pyelonephritis		1	-
- Pyelitis		1	-
- Arteritis/Periarter.		1	-
- Plaques·bacterial		1	-
- Amyloidosis		8	7
- Tubular atrophy		19	18
- Tubular casts		27	28
- Tubular dilatation		-	1
- Tub. mineralisation		5	2
- Ectasia·pelvis		1	4
- Fatty change		1	-
- Cyst(s)·cortical		15	14
URETHERS	No.Examin	-	1
URINARY BLADDER	No.Examin	50	50
- Inflammation		1	-
- Inf.·lymphoid cell		16	13
- Edema·submucosal		1	-
- Hemorrhage		1	1
- Colloid plug		29	24
TESTES	No.Examin	50	50
- Hyperpl.·Leydig cell		1	-
- Granuloma·sperm		-	1
- Amyloidosis		8	5
- Atrophy·tubular		4	4
- Mineraliz.·tubular		3	2
EPIDIDYMIDES	No.Examin	50	50
- Inflammation		1	-
- Inf.·lymphoid cell		9	8
- Oligospermia		3	2
- Aspermia		3	3
- Debris·spermatic		6	6

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

TEST ARTICLE : AE F122 006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : HOECHST

PATHOL. NO.: 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
PROSTATE	No.Examin	49	49
- Hyperplasia		1	5
- Inflammation		3	-
- Inf.·lymphoid cell		13	4*
SEMINAL VESICLES	No.Examin	50	50
- Fibrosis		-	1
- Inflammation		1	-
- Inf.·lymphoid cell		1	2
PENIS	No.Examin	-	1
PITUITARY GLAND	No.Examin	34	39
- Hyperpl.·pars dist.		1	1
- Cyst(s)·colloid		1	1
THYROID GLAND	No.Examin	49	47
- Hyperpl.·follicular		-	2
- Inflammation		4	-
- Inf.·lymphoid cell		7	4
- Amyloidosis		8	8
PARATHYROID GLANDS	No.Examin	44	41
- Inf.·lymphoid cell		-	1
- Amyloidosis		7	4
ADRENAL CORTEX	No.Examin	49	48
- Hyperpl.·foc.·A-cell		-	1
- Hyperpl.·A-cell·dif.		20	12
- Hypertrophy·cortical		5	1
- Amyloidosis		9	8
- Fatty change·focal		1	1
- Thrombosis		-	1
ADRENAL MEDULLA	No.Examin	47	46
- Hyperpl.·medullary		-	1
HEMOLYMPHORET. SYS.	No.Examin	50	49
SPLEEN	No.Examin	49	48
- Hyperpl.·marginal z.		-	1
- Megakaryocytosis		5	3
- Amyloidosis		8	5
- Atrophy		6	4
- Depletion·lymphocyte		2	-
- Erythropoesis·extra.		3	2
- Myelopoesis·extramed		3	2
BONE MARROW	No.Examin	50	50
- Granulopoesis·incre.		2	2
- Megakaryopoesis·inc.		-	2
- Congestion·sinus		2	-
- Myelophthisis·focal		4	1
THYMUS	No.Examin	26	20
- Hyperpl.·tub.+ cords		-	2
- Atrophy		1	5*
- Cyst(s)		2	1
LYMPH NODES	No.Examin	2	-
- Hyperpl.·plasma cell		1	-
- Hematopoesis·extram.		1	-

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

271

TEST ARTICLE : AE F122 006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : HOECHST

PATHOL. NO. : 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
MESENT. LYMPH NODE	No.Examin	41	42
- Hyperpl.·angiomatous		1	-
- Granulocytosis		-	1
- Histiocytosis		-	1
- Amyloidosis		8	7
- Hemorrhage		1	2
ILIAC LYMPH NODE	No.Examin	24	32
- Hyperpl.·plasma cell		1	-
- Histiocytosis·sinus		-	1
- Granulocytosis		-	2
- Megakaryocytosis		1	6
- Amyloidosis		3	2
- Hematopoesis·extram.		1	-
MANDIBULAR LYMPH NO.	No.Examin	44	43
- Inflammation		-	1
- Amyloidosis		3	3
- Ectasia·sinus		1	1
- Hemorrhage		1	-
- Thrombosis		1	1
- Hematopoesis·extram.		1	-
PAROTID GLANDS	No.Examin	49	50
- Inf.·lymphoid cell		4	3
- Amyloidosis		9	6
- Atrophy·diffuse		1	-
SUBLINGUAL GLANDS	No.Examin	46	47
- Inf.·lymphoid cell		1	1
SUBMANDIBULAR GLANDS	No.Examin	50	50
- Inf.·lymphoid cell		29	26
HARDERIAN GLANDS	No.Examin	49	49
- Inflammation		1	-
- Inf.·lymphoid cell		10	9
- Degeneration		2	1
- Hemorrhage		1	-
EXORBITAL LACR.GLDS.	No.Examin	43	39
- Inf.·lymphoid cell		13	17
- Amyloidosis		8	3
SKIN/SUBCUTIS	No.Examin	49	50
- Inflammation·dermis		2	-
- Hemorrhage		-	1
- Edema		1	1
- Cyst(s)·epidermal		1	-
SKELETAL MUSCLE	No.Examin	48	50
- Inf.·lymphoid cell		-	1
- Inf.·granulocytic c.		-	1
- Arteritis/Periarter.		1	-
- Degeneration		-	2
DIAPHRAGM	No.Examin	45	49
- Reaction·mesothelial		1	2
- Degeneration		-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

TEST ARTICLE : AE F122 006 *PATHOL. NO.*: 90004 BUB
TEST SYSTEM : MOUSE, 18 months, oral *DATE* : 19-JUL-99
SPONSOR : HOECHST *PathData® System V4.1C*

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

	SEX :			MALE
	DOSE GROUP :	C2	D4	
ORGAN/FINDING	NO. ANIMALS :	50	50	
EYES	No.Examin :	50	49	
- Degeneration·lens	:	6	4	
- Mineralization·corn.	:	1	-	
OPTIC NERVES	No.Examin :	41	35	
- Degen. myelinopathy	:	-	1	
EARS	No.Examin :	9	10	
- Hemorrhage	:	1	-	
JOINT·FEMUROTIBIAL	No.Examin :	49	50	
- Fibro-osseus lesion	:	1	2	
- Osteoporosis	:	2	-	
- Arthropathy·degener.	:	1	1	
STERNUM	No.Examin :	47	50	
- Deg.·chondromucinous	:	1	1	

*One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,*

273

TEST ARTICLE : AE F122 006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : HOECHST

PATHOL. NO.: 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
GENERAL OBSERVATIONS	No.Examin	50	50
- Autolysis severe		2	12**
- Autolysis		2	4
- Amyloidosis		3	4
CEREBRUM	No.Examin	49	50
- Mineralization		5	5
CEREBELLUM	No.Examin	47	44
MEDULLA OBLONGATA	No.Examin	44	46
- Hemorrhage		3	6
SPINAL CORD, CERVIC.	No.Examin	48	44
- Hemorrhage		4	-
SPINAL CORD, THORAC.	No.Examin	48	49
SPINAL CORD, LUMBAR	No.Examin	47	47
PERIPHERAL NERVE(S)	No.Examin	49	47
- Inf. lymphoid cell		-	1
- Degen. myelinopathy		1	-
HEART	No.Examin	50	50
- Cardiomyopathy focal		1	-
- Inflammation		1	-
- Inf. lymphoid cell		1	1
- Arteritis/Periarter.		3	-
- Amyloidosis		3	5
AORTA	No.Examin	45	48
NOSE	No.Examin	47	45
- Metapl. respiratory		1	-
- Eosinophil. globules		3	3
- Blood in nas. cavity		8	2
- Fibro-osseus lesion		1	3
LARYNX	No.Examin	36	44
- Inflammation		2	-
TRACHEA	No.Examin	45	42
- Aspiration blood		3	1
LUNGS	No.Examin	50	50
- Hyperpl. bron.-alv.		1	-
- Hyperplasia BALT		1	1
- Inf. lymphoid cell		3	-
- Granulocytosis		3	4
- Alveolar macrophages		2	-
- Amyloidosis		1	2
- Hemorrhage		12	6
- Mineralization		-	1
- Edema alveolar		-	1
MEDIASTINUM	No.Examin	2	-
- Inf. lymphoid cell		1	-

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

277

PATHOLOGY REPORT HMR Deutschland GmbH
SUMMARY TABLES

TEST ARTICLE : AE F122 006
TEST SYSTEM : MOUSE, 18 months, oral
SPONSOR : HOECHST

PATHOL. NO.: 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
TONGUE	No.Examin	50	49
- Inflammation		1	-
- Arteritis/Periarter.		2	-
- Edema		-	1
ESOPHAGUS	No.Examin	47	48
- Inf.-lymphoid cell		1	-
FORESTOMACH	No.Examin	47	48
- Inflammation		1	-
GLANDULAR STOMACH	No.Examin	47	44
- Hyperplasia		4	3
- Inflammation		1	-
- Inf.-lymphoid cell		2	4
- Amyloidosis		1	1
- Ectasia-glandular		8	4
DUODENUM	No.Examin	46	35
- Amyloidosis		2	1
JEJUNUM	No.Examin	46	35
- Hyperplasia		-	1
- Amyloidosis		2	2
ILEUM	No.Examin	40	35
- Amyloidosis		5	5
CECUM	No.Examin	45	32
- Nematode(s)		1	-
COLON	No.Examin	43	31
- Nematode(s)		3	1
RECTUM	No.Examin	42	33
- Amyloidosis		-	1
MESENTERY	No.Examin	1	5
- Inf.-lymphoid cell		-	2
LIVER	No.Examin	50	49
- Hyperplasia-hepatoc.		-	1
- Mitosis		1	-
- Inf.-lymphoid cell		30	20*
- Kupffer-cell granul.		35	22**
- Necrosis-centrilob.		1	-
- Necrosis-single cell		2	-
- Necrosis-focal		1	2
- Remodelling-lobular		-	1
- Fatty change-centri.		1	-
- Amyloidosis		3	4
- Hematopoesis-extram.		1	1
GALLBLADDER	No.Examin	44	37
- Inf.-lymphoid cell		4	7
PANCREAS	No.Examin	48	47
- Hyperpl.-islet cell		3	9
- Inf.-lymphoid cell		1	5
- Atrophy-lobular		-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

27

TEST ARTICLE : AE F122 006
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PATHOL. NO.: 90004 BUB
DATE : 19-JUL-99
PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
KIDNEYS	No.Examin	50	50
- Hyperplasia tubular		6	6
- Hypoplasia		-	1
- Inf. lymphoid cell		41	27**
- Nephropathy chr. pr.		1	3
- Amyloidosis		3	3
- Glomerulosclerosis		-	1
- Tubular atrophy		13	8
- Tubular casts		29	26
- Tubular dilatation		1	-
- Hyal. resorp. bodies		-	2
- Cyst(s) medullary		1	-
- Cyst(s) cortical		8	4
URINARY BLADDER	No.Examin	42	41
- Hyperpl. angiomatous		1	-
- Inf. lymphoid cell		25	21
OVARIES	No.Examin	50	47
- Cyst(s)		29	24
- Hemorrhage		5	2
- Amyloidosis		3	4
OVIDUCTS	No.Examin	46	42
UTERUS	No.Examin	50	50
- Hyperpl. glandular		38	34
- Arteritis/Periarter.		1	-
- Hemorrhage		1	1
- Thrombosis		-	1
- Amyloidosis		-	2
- Ectatic lumen		-	2
VAGINA	No.Examin	48	40
PITUITARY GLAND	No.Examin	41	40
- Hyperpl. pars dist.		-	1
- Hyperpl. pars inter.		1	-
- Cyst(s)		-	1
- Remn. cranio-pharyn.		1	-
THYROID GLAND	No.Examin	47	47
- Hyperpl. follicular		4	6
- Hyperpl. C-cell foc.		1	-
- Inflammation		1	3
- Inf. lymphoid cell		6	7
- Amyloidosis		3	3
PARATHYROID GLANDS	No.Examin	39	41
- Inf. lymphoid cell		2	2
- Amyloidosis		2	3
ADRENAL CORTEX	No.Examin	49	48
- Hyperpl. A-cell dif.		40	36
- Amyloidosis		3	4
ADRENAL MEDULLA	No.Examin	45	44
HEMOLYMPHORET. SYS.	No.Examin	50	50

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

276

TEST ARTICLE : AE F122 006 *PATHOL. NO.*: 90004 BUB
TEST SYSTEM : MOUSE, 18 months, oral *DATE* : 19-JUL-99
SPONSOR : HOECHST PathData® System V4.1C

NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2 50	D4 50
SPLEEN	No.Examin	49	49
- Hyperpl.·marginal z.		-	2
- Megakaryocytosis		3	8
- Amyloidosis		2	2
- Atrophy		4	7
- Depletion·lymphocyte		-	2
- Erythropoesis·extra.		3	8
- Myelopoesis·extramed		3	8
- Storage·brown pigm.		1	2
BONE MARROW	No.Examin	50	50
- Granulopoesis·incre.		3	1
- Congestion·sinus		1	2
- Myelophthisis·focal		9	9
THYMUS	No.Examin	34	28
- Hyperpl.·tub.+ cords		-	2
- Hemorrhage		2	-
- Atrophy		3	4
- Mineralization		-	1
- Cyst(s)		-	2
LYMPH NODES	No.Examin	1	-
- Hyperpl.·plasma cell		1	-
MESENT. LYMPH NODE	No.Examin	33	35
- Granulocytosis		-	1
- Megakaryocytosis		1	1
- Amyloidosis		2	2
- Hemorrhage		1	1
ILIAC LYMPH NODE	No.Examin	36	30
- Inflammation		-	1
- Hyperpl.·plasma cell		3	-
- Granulocytosis		3	4
- Megakaryocytosis		2	1
- Amyloidosis		-	1
- Hemorrhage		1	-
MANDIBULAR LYMPH NO.	No.Examin	47	40
- Hyperpl.·plasma cell		-	1
- Granulocytosis		2	1
- Megakaryocytosis		1	-
- Amyloidosis		2	2
- Hemorrhage		6	2
PAROTID GLANDS	No.Examin	50	49
- Inf.·lymphoid cell		2	1
- Amyloidosis		4	4
SUBLINGUAL GLANDS	No.Examin	50	48
- Inf.·lymphoid cell		1	-
- Amyloidosis		1	-
SUBMANDIBULAR GLANDS	No.Examin	50	49
- Inf.·lymphoid cell		21	17
- Amyloidosis		1	-
- Atrophy·focal		-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

TEST ARTICLE : AE F122 006 *PATHOL. NO.*: 90004 BUB
TEST SYSTEM : MOUSE, 18 months, oral *DATE* : 19-JUL-99
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NUMBER OF ANIMALS WITH NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

FEMALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	C2	D4
HARDERIAN GLANDS	No.Examin	50	50
- Hyperpl.-glandular		-	3
- Inf.-lymphoid cell		24	18
- Degeneration		5	3
EXORBITAL LACR.GLDS.	No.Examin	27	21
- Inf.-lymphoid cell		11	4
- Amyloidosis		-	1
- Alteration-Harderian		1	-
MAMMARY GLAND	No.Examin	46	45
- Hemorrhage		1	-
SKIN/SUBCUTIS	No.Examin	50	47
- Inflammation-dermis		2	1
- Arteritis/Periarter.		1	-
- Hyperkeratosis		1	-
SKELETAL MUSCLE	No.Examin	50	50
- Inflammation		1	-
- Inf.-lymphoid cell		-	1
- Arteritis/Periarter.		1	-
DIAPHRAGM	No.Examin	42	45
- Reaction-mesothelial		1	1
EYES	No.Examin	50	49
- Inflammation-cornea		-	1
- Atrophy-retina		3	3
- Degeneration-lens		2	1
OPTIC NERVES	No.Examin	43	39
- Degen. myelinopathy		1	-
- Atrophy		-	1
EARS	No.Examin	7	7
JOINT-FEMUROTIBIAL	No.Examin	50	49
- Fibro-osseus lesion		1	3
STERNUM	No.Examin	50	45
- Fibro-osseus lesion		4	1
- Deg. chondromucinous		-	1

One-Sided Exact Fisher Test: *) p<=0.05; **) p<=0.01; Control=C2,

Helen.Cunny@aventis.com on 12/13/2000 02:18:45 PM

To: Karlwilhelm.Muenks@aventis.com, William Dykstra/DC/USEPA/US
cc:
Subject: RE: Isoxadifen-ethyl (AE F122006) Safener

Dear Bill,
To follow up on this email and also our phone conversation, in addition to the Peto analysis, three additional statistical analysis were run. They were the Bailer and Portier method (1988) Poly-3 test which is a survival adjusted Chi-square test; an unadjusted Pearson's Chi-square test; and a Fisher's exact test. There were no statistically significant differences.
Helen

> -----Original Message-----
> From: Muenks, Karl-Wilhelm
> Sent: Tuesday, December 12, 2000 6:06 PM
> To: 'dykstra.william@epa.gov'
> Cc: 'Soltero.vera@epa.gov'
> Subject: Isoxadifen-ethyl (AE F122006) Safener
>
>
>
> Dear Bill,
>
> due to the given short deadlines, we agreed to send to you by E-Mail our
> responses to the following HED requirements for our safener
> isoxadifen-ethyl (thanks to our toxicologist Helen Cunny who finally
> managed to get the Peto analysis done because that was in fact a
> time-consuming exercise):
>
> 1. Mouse Onco: Statistical re-analysis (Peto)
> 2. Rat development study: historical control data
> 3. Dog metabolism: upgrade
> 4. In vivo cytogenetics: replacement
>
> Attached please find 4 documents, 3 in pdf format and 1 in WordPerfect
> Format, which address all above mentioned requirements. The WordPerfect
> document contains a table with results of the Peto Test, however we expect
> a more detailled table from the contract lab on 13 December, which we
> would like to forward to you, as well.
>
> After the important meetings (e.g. HIARC) have taken place, we will find
> more time to do a formal submission of the attached documents, as agreed
> upon.
>
> I hope you find attached what you need. If you have any question, please
> contact either me (919 549 2323) or Helen Cunny (919 549 2166) for more
> information.
>

27°

>
> Kind Regards
> Karl Muenks
> Aventis CropScience
>
>
>
> << File: 006_Mouse Onco Peto.PDF >> << File: 006_Peto_table.wpd >> <<
> File: 006_Dog Metabolism.pdf >> << File: 006_Mouse Micronucleus&Rat
> Terat.PDF >>
>
>
>
>

Karlwilhelm.Muenks@aventis.com on 12/13/2000 11:35:58 AM

To: William Dykstra/DC/USEPA/US
cc:
Subject: Peto Table

Bill,
attached please find the more detailled Peto table, which we just got from the lab,

Regards
Karl

<<Detailled PetoTable.WPD>>

 - Detailled PetoTable.WPD

281

Sex / Endpoint		AEF 122006 Mouse Oncogenicity Study: Treatment Group Tumor Incidence Rates and Pairwise Comparisons to Controls			
	Control Incidence	12.5 ppm	125 ppm	1250 ppm	2500 ppm
Males					
Lung Carcinoma	5.1%	10.0% 0.2765	4.0% 0.8766	8.2% 0.4304	14.0% 0.0583
Lung Adenoma	4.0%	2.0% 0.4814	0.0% 0.2371	8.2% 0.4659	0.0% 0.3165
Liver Carcinoma	7.0%	6.0% 1.000	8.0% 0.7626	8.2% 0.6427	12.0% 0.2687
Liver Adenoma	3.0%	0.0% 0.2681	2.0% 0.7711	2.0% 0.7649	2.0% 0.7630
Any Lung	9.1%	12.0% 0.5918	4.0% 0.6882	16.3% 0.2243	14.0% 0.3374
Any Liver	10.0%	6.0% 0.5876	10.0% 1.000	10.2% 0.8876	14.0% 0.4723
Females					
Lung Carcinoma	4.0%	4.0% 1.000	4.0% 1.000	0.0% 0.5079	6.1% 0.6561
Lung Adenoma	9.0%	2.0% 0.1097	4.0% 0.2753	6.0% 0.3742	4.1% 0.2702
Liver Carcinoma	0%	0% 1.000	0% 1.000	0% 1.000	0% 1.000
Liver Adenoma	1.0%	0% 0.5304	0% 0.5217	0% 0.5304	0% 0.5130
Any Lung	13.0%	6.0% 0.2031	8.0% 0.3890	6.0% 0.2026	10.2% 0.5619
Any Liver	1.0%	0% 0.5304	0% 0.5217	0% 0.5304	0% 0.5130

None statistically significant ($p>0.05$) via Peto's (1980) test.
Peto's test implemented in the MULTTEST procedure of SAS® 6.12.

282

William Dykstra
12/13/2000 08:16 AM

To: William Burnam/DC/USEPA/US@EPA, Elizabeth Doyle/DC/USEPA/US@EPA, Pamela Hurley/DC/USEPA/US@EPA, Elizabeth Mendez/DC/USEPA/US@EPA, David Nixon/DC/USEPA/US@EPA, Jess Rowland/DC/USEPA/US@EPA, Brenda Tarplee/DC/USEPA/US@EPA, Jonathan Chen/DC/USEPA/US@EPA, Ayaad Assaad/DC/USEPA/US@EPA, Stephen Dapson/DC/USEPA/US@EPA, Clark Swentzel/DC/USEPA/US@EPA, George Herndon/DC/USEPA/US@EPA
cc:
Subject: Isoxadifen-ethyl (AE F122006) Safener

Dear Friends,

Aventis, the registrant for AEF 122006, has submitted, as requested, some preliminary responses to RAB1 questions that concern the HIARC meeting on 12/14/00. Additional information may also be submitted by Aventis today. I have forwarded them to you for your perusal. Please bring the paper copy you generate to the HIARC.

Thanks,

Bill Dykstra

---------- Forwarded by William Dykstra/DC/USEPA/US on 12/13/2000 07:48 AM ----------

Karlwilhelm.Muenks@aventis.com on 12/12/2000 06:06:23 PM

To: William Dykstra/DC/USEPA/US
cc: Solter0.vera@epamail.epa.gov
Subject: Isoxadifen-ethyl (AE F122006) Safener

Dear Bill,

due to the given short deadlines, we agreed to send to you by E-Mail our responses to the following HED requirements for our safener isoxadifen-ethyl (thanks to our toxicologist Helen Cunny who finally managed to get the Peto analysis done because that was in fact a time-consuming exercise):

1. Mouse Onco: Statistical re-analysis (Peto)
2. Rat development study: historical control data
3. Dog metabolism: upgrade
4. In vivo cytogenetics: replacement

Attached please find 4 documents, 3 in pdf format and 1 in WordPerfect Format, which address all above mentioned requirements. The WordPerfect document contains a table with results of the Peto Test, however we expect a more detailled table from the contract lab on 13 December, which we would like to forward to you, as well.

After the important meetings (e.g. HIARC) have taken place, we will find

more time to do a formal submission of the attached documents, as agreed upon.

I hope you find attached what you need. If you have any question, please contact either me (919 549 2323) or Helen Cunny (919 549 2166) for more information.

Kind Regards
Karl Muenks
Aventis CropScience

<<006_Mouse Onco Peto.PDF>> <<006_Peto_table.wpd>> <<006_Dog Metabolism pdf>> <<006_Mouse Micronucleus&Rat Terat.PDF>>

 - 006_Mouse Onco Peto.PDF

 - 006_Peto_table.wpd

 - 006_Dog Metabolism.pdf

 - 006_Mouse Micronucleus&Rat Terat.PDF

294

AE F 122006 MOUSE ONCOGENICITY STUDY
MRID 44973801&44973802

EPA Request:

Conduct a Peto Analysis on the above study using a 0.05 significance level for adenomas and carcinomas both separately and combined.

Aventis Response:

The Peto analysis was conducted for liver and lung adenomas and carcinomas both separately and combined for both sexes. There were no statistically significant findings. For this data, the first animal with a tumor was found on day 75. One animal died prior to this time on day 64 and was excluded from the analysis.

This analysis was conducted by Gayle S. Bieler, Senior Statistician of the Statistics Research Division at Research Triangle Institute using Peto's (1980) test implemented in the MULTTEST procedure of SAS® 6.12.

Helen Cunny, Ph.D., D.A.B.T.
Toxicology Fellow
Aventis CropScience
PO Box 12014
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285

Sex / Endpoint	Pairwise Comparisons to Controls			
	12.5 ppm	125 ppm	1250 ppm	2500 ppm
Males				
Lung Carcinoma	NS	NS	NS	NS
Lung Adenoma	NS	NS	NS	NS
Liver Carcinoma	NS	NS	NS	NS
Liver Adenoma	NS	NS	NS	NS
Any Lung	NS	NS	NS	NS
Any Liver	NS	NS	NS	NS
Females				
Lung Carcinoma	NS	NS	NS	NS
Lung Adenoma	NS	NS	NS	NS
Liver Carcinoma	NS	NS	NS	NS
Liver Adenoma	NS	NS	NS	NS
Any Lung	NS	NS	NS	NS
Any Liver	NS	NS	NS	NS

NS = not statistically significant (p>0.05) via Peto's (1980) test.
Peto's test implemented in the MULTTEST procedure of SAS® 6.12.

AEF 122006: 18-Month Carcinogenicity Feeding Study in Mice
AVENTIS. 1999. MRID No. 44973801, 44973802