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DU PONT CENTRAL RESEARCH AND DEVELOPMENT

cc: C.F. Reinhardt

TECHNICAL FILE C-1517

August 9, 1993

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TOXICITY INFORMATION ON LEAD ACETATE FEEDING STUDIES
(Ref: Letter from K. Hatfield to HJT, 4-26-93; Telephone Conversations of 7-93)

In response to your detailed inquiry on our two-year feeding studies with lead acetate in rats, I offer the following information:

1. Two chronic lead feeding studies were conducted in rats. In Study I, rats were fed diets to which lead acetate was added at concentrations of 0, 10, 50, 100, or 500 ppm (as lead). The experimental phase of this study began on 4-14-65 and the last sacrifices took place between 5-67 and 8-67. In Study II, rats were fed diets to which lead acetate was added at concentrations of 0, 1000, or 2000 ppm (as lead). The study began on 5-24-66 and the last sacrifice occurred on 5-2-68.

2. In the preceding studies, when weekly mean dietary lead intakes were reported, the values did include background dietary lead. For example, the average lead intake for rats ingesting a diet to which 500 ppm lead was added was 548 ppm (over a two-year period).

   a.) Blood, urine, and tissue were ultimately analyzed for lead content by atomic absorption spectrophometry using a method described by E. Berman (1964) for blood and urine or by a method reported by Perkin-Elmer Corporation (1966) for tissues (See Attachment 1).

   b.) No differentiation between bound and unbound forms of lead was attempted.

3. In Study I, body weights, food consumption, and mean lead intakes were monitored weekly during the two-year feeding period. In the lead intake tables (VII and VIII) I previously sent, dietary lead intake on a mg/kg/day basis was calculated from the body weight and food consumption data. Therefore, control diets to which no lead acetate was added would have no numerical value for lead intake. On the other hand, lead measurements in the feed were periodically made but I could find no details (How many measurements over two years? How often were diets analyzed?, etc.).

   In Study II, body weights and food consumption were monitored weekly only for the first 90 days of the two-year study. Those data, in tabular and graphic form, are included here (Attachment 2). The last graph of this attachment shows the calculated average daily intake of lead (mg/kg/day) for 0, 1000, and 2000 ppm over a 90-day period. In addition, similar to my response for Study I, I could not locate specific data on periodic lead measurements in diet.

4. For information on pathology diagnoses, I am enclosing a table entitled "Incidences of Microscopic Observations in Rats" for rats sacrificed from one to two years. These tables, labeled as Attachment 3, covers rats from both Study I and Study II.

   Relative to statistical analysis in general, the preceding data were subjected to an analysis of variance to determine the significant effect of three variables (dietary lead, sex, and time) on the various quantitative responses which were measured during the two years of dietary lead administration. Statistical comparisons to historical controls (as opposed to concurrent controls) were not made. However, such comparisons were conducted in a publication (under preparation) by Dr. E. Stula, the original pathologist for the preceding studies. When a pre-publication draft is available, I will send it to you.

5. Only internal pathology personnel were originally used to assess the tissues from these studies. However, for the publication cited above, kidney lesions were sent to an NTP pathologist and others, and such information will be included in the paper.

   Archived pathology records (slides, notebooks) do exist at this time and are not slated to be destroyed.

6. During the time span of the two lead acetate studies, no specific reference historical histopathology tumor data base existed. However, in the paper in preparation (cited above), Dr. Stula will cite tumor data on 2000 control rats/sex from studies conducted over a 25-year span.

7. The only lead intake data from Study II is given in Attachment 2. No tables similar to Tables VII and VIII (for Study I) were located. Food consumption measurements for Study II were only conducted for the first 90 days of the two-year feeding period.

8. Blood lead levels were serially measured in rats throughout Study I and only terminally in Study II. For Study I, the table below summarizes those blood lead measurements (as µg/ml) from lab notebooks:

DOSE LEVEL OF Pb (ppm)	BLOOD LEAD (µg/ml)				
FEMALES					
	3 mo.	6 mo.	12 mo.	18 mo.	24 mo.
0	0.0	0.026	0.0	0.006	0.123
0	0.0	0.0	0.0	0.0	0.153
10	0.0	0.0	0.10	0.06	0.121
50	0.0	0.0	0.17	0.09	0.203
100	0.20	--	0.20	0.14	0.400
500	0.25	0.22	0.60	0.59	0.790
MALES					
0	0.0	0.025	0.03	0.05	0.102
0	0.25	0.0	0.03	0.03	0.121
10	0.0	0.063	0.10	0.06	0.98
50	0.0	0.029	0.14	0.09	0.168
100	0.0	0.0	0.17	0.24	0.302
500	0.18	0.38	0.62	0.53	0.761

Zero levels were below limits of detection (0.01 µg/ml)

For Study II, blood lead levels were measured in rats at the final sacrifice (24 months) only:

For General Information

K. Hatfield

Experimental Design for Toxicity of Lead Acetate in Rats and Dogs

Study Species	Gp.	Age at Start (Days)	Lead Added to Diet (ppm), a	Lead Anal. in Diet (ppm)	No. Male	No. Female	Interim Sac. (Mos.)	Terminal Sac. (Mos.)	Repro. Studies	Blood and Urine Anal. (Mos.), b	Tissue Lead Anal (Mos.)
1 Dog	I	365-730	0	2	4	4	No	24	No	1,2,3,6, 9,12,15, 18,21,24	12,24
	II	"	10	16	"	"	"	"	"	"	24
	III	"	50	57	"	"	"	"	"	"	"
	IV	"	100	155	"	"	"	"	"	"	"
	V	"	500	576	"	"	12	"	"	"	12,24
1 Rat	I	34	0	5	50	50	3,6, 12,18	"	Yes	"	3,6,12 15,18,24
	IA	"	0	5	"	"	"	"	No	"	"
	II	"	10	18	"	"	"	"	Yes	"	"
	III	"	50	62	"	"	"	"	"	"	"
	IV	"	100	141	"	"	"	"	"	"	"
	V	"	500	548	"	"	"	"	No	"	"
11 Rat	I	"	0	3	20	20	No	"	Yes	1,2,3, 12,18,24	24
	II	"	1000	1130	"	"	"	"	"	"	"
	III	"	2000	2102	"	"	"	"	"	"	"

Code: a = calculated on a basis of actual lead (56.6% of lead acetate)
b = see Table 4 for various tests performed

ATTACHMENT 1

ROUGH DRAFT

April 9,1968

RAT TISSUE LEAD

The tissues were placed in individual plastic bags and frozen on solid carbon dioxide immediately following removal from the animal and then stored at -4° C. At the time of analysis, the samples were brought to room temperature, weighed into 35 milliliter Kjeldahl flasks and digested with 5 milliliters of a concentrated sulfuric-nitric acid solution (1:2 1:4) followed by 2 milliliters of a sulfuric-perchloric acid solution (1:1). After the digestion was completed, all nitrate and perchlorate were driven off by heating. The samples were diluted and an aliquot was taken for analysis by atomic absorption spectroscopy. The lead was extracted into an organic solvent with a chelating agent without pH adjustment and analyzed according to the methods recommended by the Perkin-Elmer Corporation (1). Tissues taken at interim periods were pooled by groups; sample size and dilution were chosen to obtain one to ten micrograms of lead in the final aliquot. Livers from the animals remaining at the end of the experiment were analyzed individually and the kidneys were combined within groups in order to obtain an adequate sample.

Bones were stripped of soft tissue (cartilage caps remained), crushed, extracted in a Soxhlet with an ethyl alcohol-diethyl ether solution (1:1), dried and weighed into flasks. Digestion and analysis were similar

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to soft tissue. Blood and urine were analyzed by the method described by Berman (2). Samples were pooled by groups at the interim sacrifices and analyzed individually at the end of the experiment.

Feed and feces were dried, ground through a 20 mesh screen and analyzed by the method described for soft tissue. Hair was washed with acetone, water, then acetone again, dried, ground through a 20 mesh screen and treated the same as soft tissue.

Standards containing 1 to 10 micrograms of lead per milliliter were prepared from lead nitrate in 1 normal sulfuric acid. One milliliter of each was chelated and extracted into methyl-isobutyl Ketone without pH adjustment and aspirated into the flame. These standards were used for all digested tissue as there was no appreciable difference between standards prepared in 1 normal sulfuric acid and those prepared in 0.1 normal sulfuric acid. Standards for blood and urine samples were prepared according to Berman (2).

The limit of measurability for digested samples was approximately 0.1 microgram per gram while that of blood and urine was 0.1 microgram per 10 milliliters. Only a single analysis of each sample was performed, but samples containing added lead were included with each batch of tissues. When recovery of added lead was less than 85% the entire batch was re-analyzed.

(1) Analytical Methods for Atomic Absorption Spectroscopy. The Perkin-Elmer Corporation, Norwalk, Conn., 1966.

(2) Berman, E. Atomic Absorption Newsletter 3(9): 111, 1964.

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ATTACHMENT #7

Average Body Heights and Average Height Gains of Male and Female Rats Fed Various Levels of Pb

Days on Test	Males I Control	Males II 0.1% Pb	Males III 0.2% Pb	Females I Control	Females II 0.1% Pb	Females III 0.2% Pb
Average Body Height (gm)						
0	117	117	117	107	107	107
7	165	158	147	136	132	121
14	216	205	193	160	158	147
21	271	254	239	186	182	168
28	312	296	278	199	200	181
35	344	327	305	213	214	193
42	379	361	344	232	230	208
49	408	386	364	242	241	220
56	433	407	388	252	250	227
63	457	424	406	257	258	233
70	462	431	409	261	262	237
77	485	456	432	272	273	247
84	509	476	455	283	284	256
91	516	479 434	466	282	283	256
Average Height Gain (gms)						
0-7	48	41	30	29	25	14
7-14	51	47	46	24	26	26
14-21	55	49	46	26	24	21
21-28	41	42	39	13	18	13
28-35	32	31	27	14	14	12
35-42	35	34	39	19	16	15
42-49	27	25	20	10	11	12
49-56	25	21	24	10	9	7
56-63	24	17	18	7	8	6
63-70	5	7	3	2	4	4
70-77	23	25	23	11	11	10
77-84	24	20	23	11	11	9
84-91	7	8	11	-1	-1	0

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Average Daily Food Consumption and Food Efficiency of Male and Female Rats Fed Various Levels of

	Males			Females		
	I	II	III	I	II	III
Days on Test	Control	0.1% Pb	0.2% Pb	Control	0.1% Pb	0.2% Pb
Average Daily Food Consumption (gms)						
0-7	17.6	16.3	15.7	14.8	14.0	13.1
7-14	20.5	18.4	19.8	16.8	14.8	15.5
14-21	22.6	22.1	21.4	15.6	15.6	15.3
21-28	23.8	23.6	22.8	16.0	17.1	16.2
28-35	23.9	23.8	23.7	16.1	17.1	15.8
35-42	23.8	23.6	26.4	16.8	17.4	14.1
42-49	24.5	24.7	23.9	17.0	17.3	15.5
49-56	24.7	24.0	23.8	17.4	16.9	15.2
56-63	24.5	23.4	23.8	17.4	16.9	15.2
63-70	23.4	23.2	22.0	17.0	17.0	16.2
70-77	23.7	24.1	23.8	16.9	16.6	15.0
77-84	23.7	23.8	24.2	16.4	16.0	15.0
84-91	23.8	23.8	24.2	15.9	15.7	15.4
Grams Height Gain / Gram Food Consumed						
0-7	.39	.36	.27	.28	.25	.15
7-14	.55	.36	.33	.20	.25	.24
14-21	.35	.32	.31	.24	.22	.20
21-28	.25	.25	.24	.12	.15	.11
28-35	.19	.18	.16	.12	.12	.11
35-42	.21	.20	.21	.16	.13	.15
42-49	.17	.15	.12	.08	.09	.11
49-56	.14	.12	.14	.08	.08	.11
56-63	.14	.10	.11	.06	.07	.06
63-70	.04	.04	.02	.02	.03	.04
70-77	.14	.15	.14	.09	.09	.10
77-84	.14	.12	.14	.10	.10	.08
84-91	.04	.05	.06	0	0	0

Fig 5 : GROWTH RESPONSE OF RATS FED LEAD ACETATE

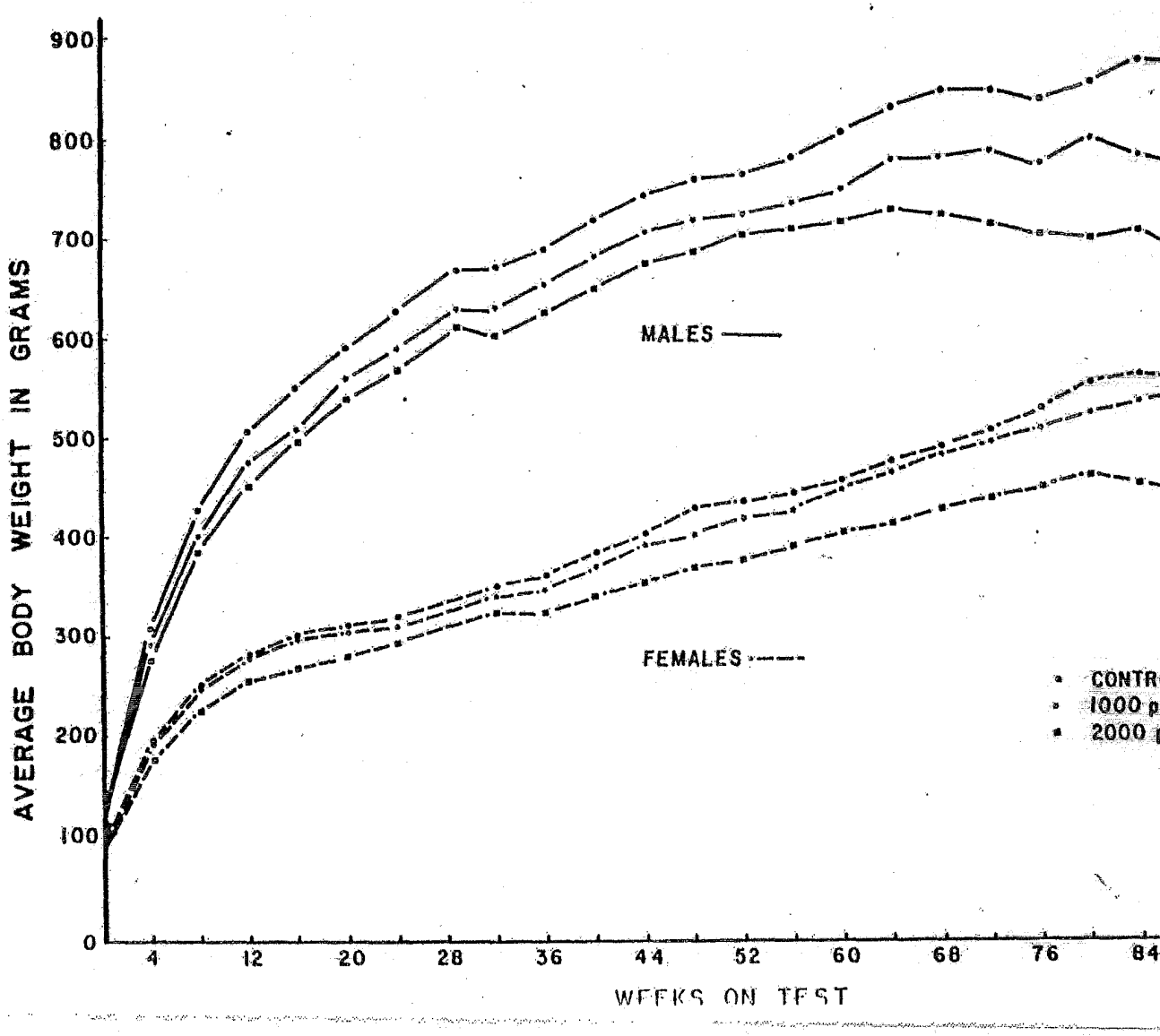

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Fig. 11: STUDY II: AVERAGE DAILY FOOD CONSUMPTION OF MALE AND FEMALE RATS FED VARIOUS LEVELS OF Pb

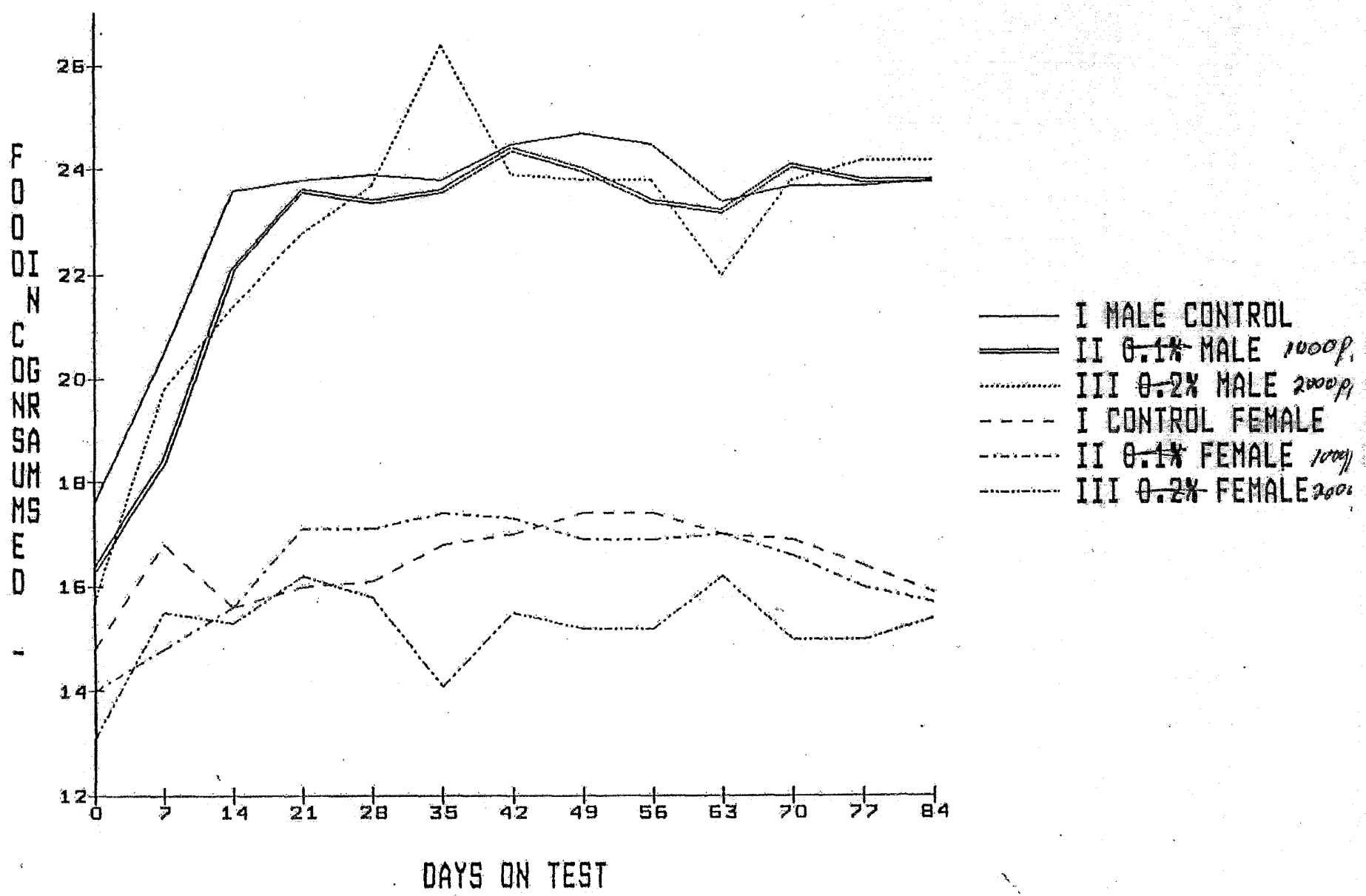

Fig.12: STUDY III: AVERAGE DAILY INTAKE OF Pb FED TO RATS
(mg/kg/day)

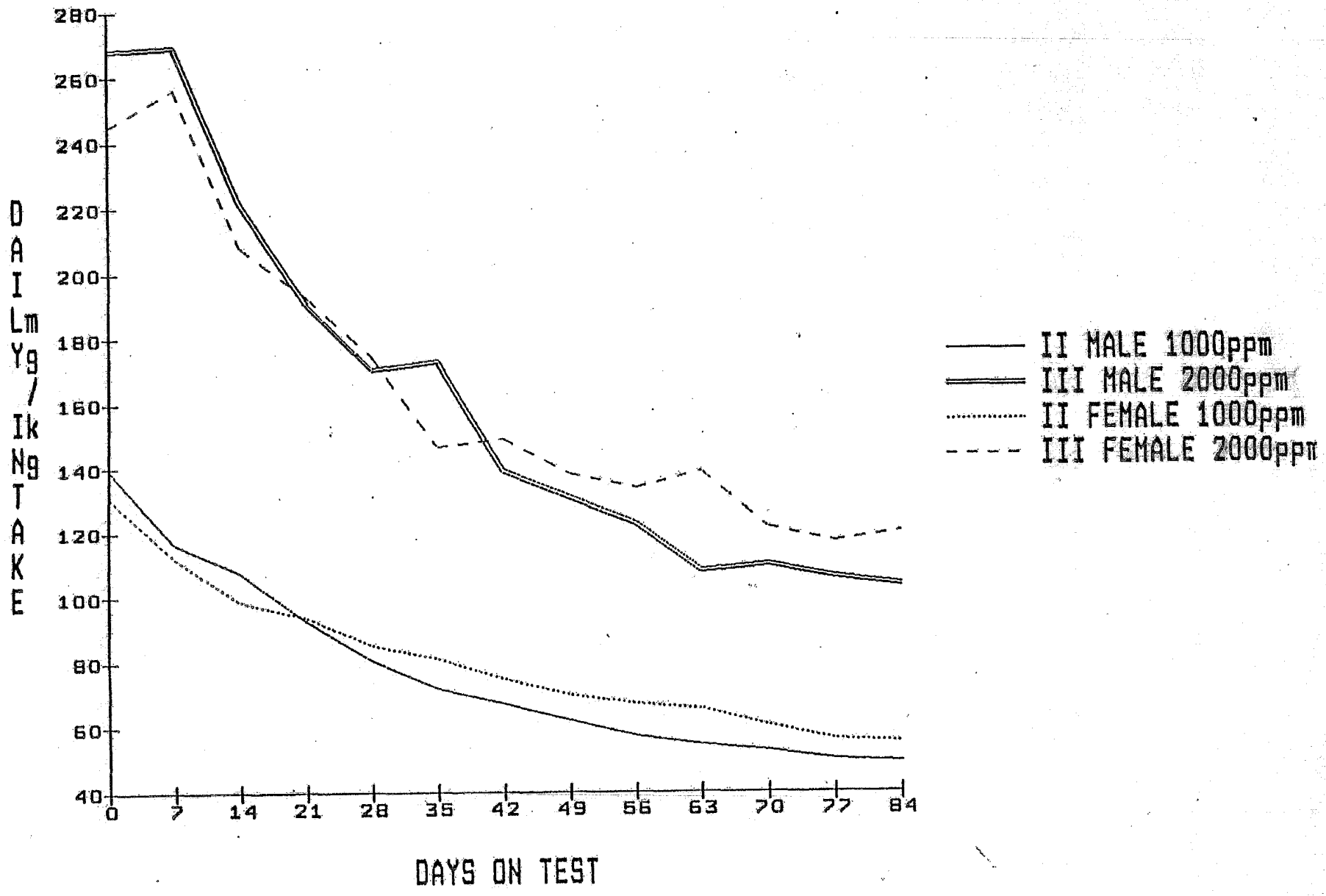

TABLE 8
STUDY I: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 738)

TISSUE/LESION	GROUP DESIGNATION:	1	IA	II	III	IV	V
	DOSE (PPM):	0	0	10	50	100	500
	NUMBER IN GROUP:	42	41	41	41	41	41
KIDNEYS		39	39	19a	20a	39	40
* PRIMARY RENAL TUBULE TUMOR [ANY TYPE]		-	2	-	-	-	3
*B: RENAL TUBULE ADENOMA		-	2	-	-	-	1
*M: RENAL TUBULE CARCINOMA		-	-	-	-	-	1
*M: RENAL TUBULE CARCINOMA [META. MULTIPLE ORGANS]		-	-	-	-	-	1
*X: LYMPHOMA		1	1	-	1	1	-
ARTERITIS		4	4	2	-	5	5
GLOMERULOPATHY,GLOBAL,DIFFUSE		8	11	1	3	8	14
HYPERPLASIA,ATYPICAL,PROXIMAL TUBULE		8	8	2	2	7	21 *
HYPERPLASIA,SIMPLE,PROXIMAL TUBULE		29	29	13	13	27	34
INTRANUCLEAR INCLUSIONS,PROXIMAL TUBULE		-	-	-	-	-	25 *
KARYOMEGALY/CYTOMEGALY,PROXIMAL TUBULE		-	-	-	-	-	30 *
METAPLASIA/HYPERPLASIA,BOWMANS CAPSULE		3	4	-	1	2	12 *
NEPHROPATHY [ANY TYPE]		38	36	18	18	36	38
NEPHROPATHY, SLIGHT		8	6	4	1	6	5
NEPHROPATHY, MILD		12	6	5	9	14	9
NEPHROPATHY, MODERATE		11	15	8	7	9	16
NEPHROPATHY, SEVERE		7	9	1	1	7	8
PYELITIS		4	2	1	-	3	-
THROMBOSIS,RENAL VEIN		2	3	-	1	2	4
TRANSITIONAL CELL HYPERPLASIA,PELVIS		6	3	1	1	4	1
NON-RENAL TUMORS		38	36	15	18	37	36
*B: ADENOMA C-CELL,THYROID		2	-	-	-	1	1
*B: ADENOMA,ADRENAL CORTEX		-	-	-	-	1	-
*B: ADENOMA,ISLET CELL		1	-	-	-	-	-
*B: ADENOMA,PITUITARY		5	7	2	1	8	4
*B: ADENOMA,SEBACEOUS CELL,SKIN		-	1	-	-	-	-
*B: ADENOMA,SEMINAL VESICLES		1	-	-	-	-	-
*B: FIBROADENOMA,MAMMARY		2	-	-	1	1	2
*B: FIBROMA,CECUM		-	-	-	-	1	-
*B: FIBROMA,SKIN		3	-	1	-	1	-
*B: FOLLICULAR CELL TUMOR,THYROID		1	-	-	-	1	-
*B: LIPOMA,MEDIASTINUM		1	-	-	-	-	-
*B: PAPILLOMA,SKIN		-	2	-	-	1	-
*B: PAPILLOMA,STOMACH		-	-	-	-	1	-
*B: PHEOCHROMOCYTOMA,ADRENAL		-	1	-	-	1	-
*M: ASTROCYTOMA,BRAIN		-	-	-	-	1	-
*M: CARCINOMA,ISLET CELL		1	-	-	-	-	-
*M: CARCINOMA,SQUAMOUS CELL,SKIN,FACE		-	1	-	-	-	-
*M: FIBROSARCOMA,SKIN		-	-	1	1	1	1

TABLE 8 (continued)
STUDY I: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 738)

TISSUE/LESION	GROUP DESIGNATION:	I	IA	II	III	IV	V	
	DOSE (PPM):	0	0	10	50	100	500	
	NUMBER IN GROUP:	42	41	41	41	41	41	
NON-RENAL TUMORS (cont'd)		38	36	15a	18a	37	36	
*M: HEMANGIOENDOTHELIOMA, SPLEEN		-	-	-	-	1	-	
*M: HEPATOCELLULAR CARCINOMA, LIVER		1	-	-	-	-	1	
*M: LIPOSARCOMA, MEDIASTINUM		-	1	-	-	-	-	
*M: LYMPHOMA, MULTIPLE ORGANS		1	1	-	1	-	-	
*M: MESOTHELIOMA, PERITONEUM, TUNICA VAGINALIS		-	-	-	-	1	-	
*M: MESOTHELIOMA, PLEURA		1	-	-	-	1	-	
*M: PHEOCHROMOCYTOMA, ADRENAL		-	2	-	-	-	-	
*M: THYMOMA		-	1	-	-	-	-	
*X: HISTIOCYTIC SARCOMA, MULTIPLE ORGANS		-	-	-	-	1	2	
*X: LYMPHOMA, MULTIPLE ORGANS		-	-	-	-	1	-	
SELECTED LESIONS		39	37	15	22	37	36	
ARTERITIS, MESENTERY		6	8	2	-	7	7	
ARTERITIS, TESTES		14	12	2	4	11	14	
CAUSE OF DEATH		42	41	41	41	41	41	
NEPHROPATHY		8	10	3	4	7	19	*
12-MONTH SACRIFICE		6	5	5	6	4	5	
18-MONTH SACRIFICE		6	6	6	6	6	5	
24-MONTH SACRIFICE		12	13	13	11	14	6	*b
ABSCESS, LEG		-	-	-	-	-	1	
ASTROCYTOMA, BRAIN		-	-	-	-	1	-	
DIAPHRAGMATIC HERNIA, LIVER		-	-	-	-	-	1	
HEMANGIOENDOTHELIOMA, SPLEEN		-	-	-	-	1	-	
HISTIOCYTIC SARCOMA, MULTIPLE ORGANS		-	-	-	-	-	2	
INFLAMMATION, MIDDLE EAR		-	-	-	1	1	-	
LIPOSARCOMA, MEDIASTINUM		-	1	-	-	-	-	
LYMPHOMA, MULTIPLE ORGANS		-	-	-	-	1	-	
MAMMARY TUMOR		1	-	-	-	1	-	
MESOTHELIOMA, PLEURA		1	-	-	-	1	-	
NOT DETERMINED		1	-	7	4	-	1	
NOT DETERMINED, ADVANCED AUTOLYSIS		3	4	3	7	4	2	
PHEOCHROMOCYTOMA, ADRENAL		-	1	-	-	-	-	
PITUITARY TUMOR		3	1	2	1	2	2	
PNEUMONIA		1	-	-	-	-	3	
PYELITIS, KIDNEY		2	-	-	-	-	-	
RENAL TUMOR AND NEPHROPATHY		-	-	-	-	-	2	
SKIN TUMOR		-	1	2	1	-	-	

TABLE 8 (continued)
STUDY I: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 738)

TISSUE/LESION	GROUP DESIGNATION:	I	IA	II	III	IV	V
	DOSE (PPM):	0	0	10	50	100	500
	NUMBER IN GROUP:	42	41	41	41	41	41

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o TUMOR CODES: *B = BENIGN; *M = MALIGNANT (PRIMARY); *X = MALIGNANT (METASTATIC/MULTICENTRIC)
- o a = ALL TISSUES COULD NOT BE LOCATED.
- o b = 6 SURVIVORS OF GROUP WERE SACRIFICED 3 WEEKS PRIOR TO SCHEDULED TERMINAL SACRIFICE IN ORDER TO ASSURE SUFFICIENT GOOD QUALITY SECTIONS.
- o * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP USING FISHER'S EXACT TEST, $p < 0.05$.

TABLE 9
STUDY I: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 748)

TISSUE/LESION	GROUP DESIGNATION:	I	IA	II	III	IV	V	
	DOSE (PPM):	0	0	10	50	100	500	
	NUMBER IN GROUP:	41	41	41	42	42	40	
KIDNEYS		40	41	11a	16a	42	39	
* PRIMARY RENAL TUBULE TUMOR [ANY TYPE]		1	-	-	-	1	-	
*B: LIPOMA,UNILATERAL		1	-	-	-	-	-	
*B: RENAL TUBULE ADENOMA,UNILATERAL		1	-	-	-	1	-	
*M: MESENCHYMAL CELL TUMOR		-	-	-	-	-	1	
*X: HISTIOCYTIC SARCOMA,METASTATIC SITE		1	-	-	-	-	-	
ARTERITIS		-	-	-	-	2	2	
GLOMERULOPATHY,GLOBAL,DIFFUSE		2	2	1	1	3	5	
HYPERPLASIA,ATYPICAL,PROXIMAL TUBULE		1	1	2	1	3	7	*
HYPERPLASIA,SIMPLE,PROXIMAL TUBULE		13	8	4	3	16	19	
INTRANUCLEAR INCLUSIONS,PROXIMAL TUBULE		-	-	-	-	-	38	*
KARYOMEGALY/CYTOMEGALY,PROXIMAL TUBULE		-	-	-	-	-	30	*
METAPLASIA/HYPERPLASIA,BOWMANS CAPSULE		-	-	-	-	-	-	
NEPHROPATHY, [ANY TYPE]		25	24	9	10	29	27	
NEPHROPATHY, SLIGHT		13	15	4	7	11	13	
NEPHROPATHY, MILD		9	3	3	2	13	7	
NEPHROPATHY, MODERATE		3	6	1	1	3	6	
NEPHROPATHY, SEVERE		-	-	1	-	2	1	
PYELITIS		1	-	-	-	1	-	
THROMBOSIS,RENAL VEIN		1	-	-	-	1	1	
TRANSITIONAL CELL HYPERPLASIA,PELVIS		5	2	1	-	1	2	
NON-RENAL TUMORS		41	41	7	8	42	38	
*B: ADENOMA,C-CELL,THYROID		3	-	-	-	-	1	
*B: ADENOMA,DUODENUM		-	-	-	-	-	1	
*B: ADENOMA,ISLET CELL		1	-	-	-	-	-	
*B: ADENOMA,PITUITARY		8	14	-	1	12	12	
*B: ADENOMA,UTERUS		1	-	-	-	-	-	
*B: FIBROADENOMA,MAMMARY		15	22	2	1	12	19	
*B: FIBROMA,SKIN		-	-	-	-	1	-	
*B: FIBROMA,UTERUS		1	-	-	-	-	-	
*B: FOLLICULAR CELL TUMOR,THYROID		1	-	-	-	-	-	
*B: GANGLIONONEUROMA,ADRENAL		-	1	-	-	-	-	
*B: LEIOMYOMA,UTERUS		1	-	-	-	-	-	
*B: POLYP,UTERUS		2	-	-	-	4	-	
*M: ADENOCARCINOMA,C-CELL,THYROID		-	-	-	-	-	1	
*M: ADENOCARCINOMA,MAMMARY		1	2	-	-	-	1	
*M: ADENOCARCINOMA,UTERUS		-	-	-	-	1	-	
*M: FIBROSARCOMA,ILEUM		-	-	-	1	-	-	
*M: FIBROSARCOMA,SKIN		1	1	-	-	1	1	
*M: HEPATOCELLULAR CARCINOMA,LIVER		-	-	-	-	1	-	
*M: LIPOSARCOMA,MESENTERY		-	-	-	-	-	1	

TABLE 9 (continued)
STUDY I: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 748)

TISSUE/LESION	GROUP DESIGNATION:	I	IA	II	III	IV	V
	DOSE (PPM):	0	0	10	50	100	500
	NUMBER IN GROUP:	41	41	41	42	42	40
NON-RENAL TUMORS (cont'd)		41	41	7	8	42	38
*M: OSTEOGENIC SARCOMA,SKIN		-	-	-	-	1	-
*M: SQUAMOUS CELL CARCINOMA,LIP		1	-	-	-	-	-
*M: ZYMBAL GLAND TUMOR		-	-	-	-	-	1
*X: HISTIOCYTIC SARCOMA,MULTIPLE ORGANS		3	1	-	-	1	1
SELECTED LESIONS		41	41	7a	8a	42	39
ARTERITIS,MESENTERY		1	1	2	-	2	1
CAUSE OF DEATH		41	41	41	42	42	40
NEPHROPATHY		1	2	1	-	2	2
12-MONTH SACRIFICE		5	5	5	6	6	4
18-MONTH SACRIFICE		6	6	6	7	6	6
24-MONTH SACRIFICE		16	13	16	15	17	14
ABSCESS,MEDIASTINUM		-	-	-	-	1	-
ABSCESS,MIDDLE EAR		-	1	-	-	1	-
FIBROSARCOMA,ILLEUM		-	-	-	1	-	-
FIBROSARCOMA,SKIN		1	-	-	-	1	1
HISTIOCYTIC SARCOMA,MULTIPLE ORGANS		3	1	-	-	1	-
HYPERPLASIA,ENDOMETRIUM		-	1	-	-	-	-
LIPOSARCOMA,MESENTERY		-	-	-	-	-	1
MAMMARY TUMOR		5	4	1	4	2	5
NOT DETERMINED		-	-	7	4	-	-
NOT DETERMINED,AUTOLYSIS ADVANCED		-	-	2	-	-	1
PITUITARY TUMOR		6	8	3	7	5	8
PNEUMONIA		-	-	-	-	1	-
PYOMETRA		-	-	-	-	-	1
TUMOR,PERITONEAL CAVITY		-	-	-	1	-	-
ZYMBAL GLAND TUMOR		-	-	-	-	-	1

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o TUMOR CODES: *B = BENIGN; *M = MALIGNANT (PRIMARY); *X = MALIGNANT (METASTATIC/MULTICENTRIC)
- o a = ALL TISSUES COULD NOT BE LOCATED.
- o * = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING FISHER'S EXACT TEST, $p < 0.05$.

TABLE 10
STUDY II: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 706)

TISSUE/LESION	GROUP DESIGNATION: I DOSE (PPM): 0 NUMBER IN GROUP: 18	II 1000 20	III 2000 20
KIDNEYS	18	19	19
* PRIMARY RENAL TUBULAR TUMOR [ANY TYPE]	-	9 *	16 *
*B: RENAL TUBULE ADENOMA	-	1	2
*M: RENAL TUBULE CARCINOMA	-	5 *	9 *
*M: RENAL TUBULE CARCINOMA, ANAPLASTIC	-	2	1
*M: RENAL TUBULE CARCINOMA, ANAPLASTIC [META. MULTIPLE ORGANS]	-	1	4
*M: RENAL TUBULE CARCINOMA, BILATERAL	-	1	-
*M: RENAL TUBULE CARCINOMA, MULTIPLE, BILATERAL	-	-	1
ARTERITIS	4	1	2
GLOMERULOPATHY, GLOBAL, DIFFUSE	5	8	2
HYPERPLASIA, ATYPICAL, PROXIMAL TUBULE	5	14 *	17 *
HYPERPLASIA, SIMPLE, PROXIMAL TUBULE	12	17	14
INTRANUCLEAR INCLUSIONS, PROXIMAL TUBULE	-	12 *	9 *
KARYOMEGALY/CYTOMEGALY, PROXIMAL TUBULE	-	10 *	4
METAPLASIA/HYPERPLASIA, BOWMANS CAPSULE	5	13 *	6
NEPHROPATHY [ANY TYPE]	17	18	19
NEPHROPATHY, SLIGHT	4	-	1
NEPHROPATHY, MILD	6	7	5
NEPHROPATHY, MODERATE	5	9	3
NEPHROPATHY, SEVERE	2	2	10 *
PYELITIS	1	2	-
THROMBOSIS, RENAL VEIN	-	-	1
TRANSITIONAL CELL HYPERPLASIA, PELVIS	2	1	-
NON-RENAL TUMORS	18	18	19
*B: ADENOMA, C-CELL, THYROID	-	1	-
*B: ADENOMA, ISLET CELL	-	-	1
*B: ADENOMA, LUNG	1	-	-
*B: ADENOMA, PITUITARY	2	1	2
*B: FIBROADENOMA, MAMMARY	-	1	-
*M: CARCINOMA, SEBACEOUS CELL, SKIN	1	-	-
*M: FIBROSARCOMA, SKIN	-	1	2
*M: HEPATOCELLULAR CARCINOMA, LIVER	-	1	-
*X: LYMPHOMA, MULTIPLE ORGANS	1	-	-
SELECTED LESIONS	18	19	19
ARTERITIS, MESENTERY	4	4	5
ARTERITIS, TESTES	6	7	4
CAUSE OF DEATH	18	20	20
24-MONTH SACRIFICE	10	10	4

TABLE 10 (continued)
STUDY II: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 706)

TISSUE/LESION	GROUP DESIGNATION: I DOSE (PPM): 0 NUMBER IN GROUP: 18	II 1000 20	III 2000 20
CAUSE OF DEATH (cont'd)	18	20	20
HEMORRHAGE,LUNG	1	-	-
LYMPHOMA,MULTIPLE ORGANS	1	-	-
NECROSIS,LIVER	1	-	-
NEPHROPATHY/RENAL TUMOR	3	8	14 *
NOT DETERMINED	-	2	-
NOT DETERMINED,ADVANCED AUTOLYSIS	-	-	1
PITUITARY TUMOR	2	-	1

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o TUMOR CODES: *B = BENIGN; *M = MALIGNANT (PRIMARY); *X = MALIGNANT (METASTATIC/MULTICENTRIC).
- o * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP USING FISHER'S EXACT TEST, $p < 0.05$.

TABLE 11
STUDY II: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 709)

TISSUE/LESION	GROUP DESIGNATION: I DOSE (PPM): 0 NUMBER IN GROUP: 19	II 1000 20	III 2000 20
KIDNEYS	16	19	20
* PRIMARY RENAL TUBULE TUMOR [ANY TYPE]	-	-	2
*B: RENAL TUBULE ADENOMA	-	-	1
*B: RENAL TUBULE,ADENOMA,MULTIPLE	-	-	1
*M: RENAL TUBULE CARCINOMA	-	-	1
*X: LYMPHOMA	-	2	-
ARTERITIS	-	-	2
GLOMERULOPATHY,GLOBAL,DIFFUSE	1	-	2
HYPERPLASIA,ATYPICAL,PROXIMAL TUBULE	-	5 *	13 *
HYPERPLASIA,SIMPLE,PROXIMAL TUBULE	4	12 *	19 *
INTRANUCLEAR INCLUSIONS,PROXIMAL TUBULE	-	19 *	20 *
KARYOMEGALY/CYTOMEGALY,PROXIMAL TUBULE	-	19 *	20 *
METAPLASIA/HYPERPLASIA,BOWMANS CAPSULE	-	1	1
NEPHROPATHY [ANY TYPE]	8	14	20 *
NEPHROPATHY, SLIGHT	5	8	5
NEPHROPATHY, MILD	2	4	10 *
NEPHROPATHY, MODERATE	1	2	4
NEPHROPATHY, SEVERE	-	-	1
TRANSITIONAL CELL HYPERPLASIA,PELVIS	1	-	1
NON-RENAL TUMORS	18	20	20
*B: ADENOMA,PITUITARY	6	4	4
*B: FIBROADENOMA,MAMMARY	10	11	9
*B: GRANULOSA CELL TUMOR,OVARY	-	-	1
*B: LIPOMA,PERITONEAL	-	-	1
*B: LIPOMA,SUBCUTIS	1	-	-
*B: PAPILLOMA,SKIN	-	-	1
*M: ADENOCARCINOMA,MAMMARY	-	2	1
*M: FIBROSARCOMA,SKIN	-	1	-
*M: HISTIOCYTIC SARCOMA,LIVER	-	-	1
*X: LYMPHOMA,MULTIPLE ORGANS	-	2	-
SELECTED LESIONS	18	20	20
ARTERITIS,MESENTERY	1	-	3
CAUSE OF DEATH	19	20	20
24-MONTH SACRIFICE	13	10	13
FIBROSARCOMA,SKIN	-	1	-
HISTIOCYTIC SARCOMA,LIVER	-	-	1
LYMPHOMA,MULTIPLE ORGANS	-	2	-
MAMMARY TUMOR	3	5	3
NEPHROPATHY/RENAL TUMOR	-	-	2

TABLE II (continued)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS/998

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 709)

TISSUE/LESION	GROUP DESIGNATION: I DOSE (PPM): 0 NUMBER IN GROUP: 19	II 1000 20	III 2000 20
CAUSE OF DEATH (cont'd)	19	20	20
NOT DETERMINED,ADVANCED AUTOLYSIS	1	-	-
PITUITARY TUMOR	2	1	-
PNEUMONIA,INHALATION	-	-	1
UTERINE PROPLAPSE	-	1	-

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o TUMOR CODES: *B = BENIGN; *M = MALIGNANT (PRIMARY); *X = MALIGNANT (METASTATIC/MULTICENTRIC).
- o * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP USING FISHER'S EXACT TEST, $p < 0.05$.

TABLE 12
STUDY III: INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

(ANIMALS NECROPSIED FROM DAY 353 TO DAY 401)

TISSUE/LESION	GROUP DESIGNATION: I DOSE (PPM): 0 NUMBER IN GROUP: 10	II 5000 10
KIDNEYS	10	10
* PRIMARY RENAL TUBULE TUMOR [ANY TYPE]	-	4 *
*M: RENAL TUBULE CARCINOMA	-	3
*M: RENAL TUBULE CARCINOMA,ANAPLASTIC	-	1
HYPERPLASIA,ATYPICAL,PROXIMAL TUBULE	-	8 *
HYPERPLASIA,SIMPLE,PROXIMAL TUBULE	3	10 *
INTRANUCLEAR INCLUSIONS,PROXIMAL TUBULE	-	10 *
KARYOMEGALY/CYTOMEGALY,PROXIMAL TUBULE	-	10 *
METAPLASIA/HYPERPLASIA,BOWMANS CAPSULE	-	7 *
NEPHROPATHY [ANY TYPE]	10	10
NEPHROPATHY, SLIGHT	6	1 *
NEPHROPATHY, MILD	1	9 *
NEPHROPATHY, MODERATE	2	-
NEPHROPATHY, SEVERE	1	-
PYELITIS	-	1
NON-RENAL TUMORS	9	10
*B: HEMANGIOMA,MESENTERIC LYMPH NODE	-	1
SELECTED LESIONS	9	10
ARTERITIS,MESENTERY	-	-
ARTERITIS,TESTES	-	-
CAUSE OF DEATH	10	10
13-MONTH SACRIFICE	9	10
NEPHROPATHY	1	-

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o TUMOR CODES: *B = BENIGN; *M = MALIGNANT (PRIMARY)
- o * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP USING FISHER'S EXACT TEST, $p < 0.05$.